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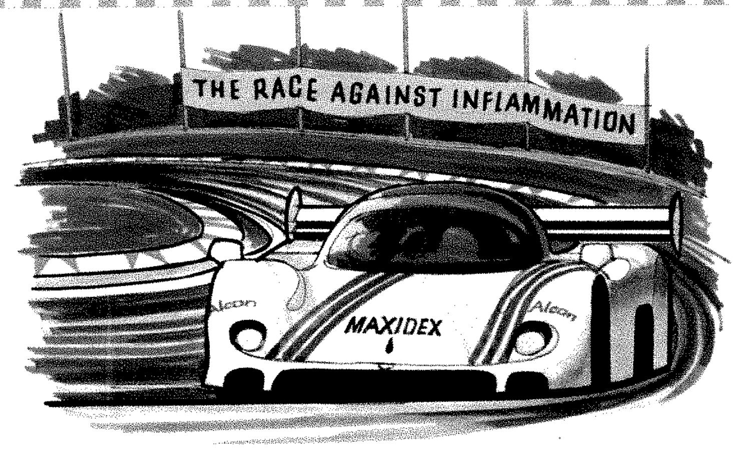

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Long-term follow-up of retinal blood flow in diabetes using the blue light entoptic phenomenon

TIM RIMMER, TIMOTHY J FALLON, AND EVA M KOHNER

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SUMMARY The blue light entoptic phenomenon was used to measure retinal blood flow in 87 diabetics and 10 normal controls in a longitudinal study. The time interval between the initial and final studies was 21–39 months (mean 31·4). The retinal blood flow velocity did not change in the 10 subjects in the control group nor in those nine patients with no retinopathy, all but one of whom remained free of retinal lesions. In the 24 with background retinopathy the flow velocity fell significantly from 0·71 (SD 0·35) mm/s to 0·48 (0·13) mm/s ($p<0·01$). The velocity also decreased in the preproliferative group of 16 patients from 0·62 (0·39) mm/s to 0·41 (0·14) mm/s ($p<0·05$). The retinopathy status changed in 11 of this group. In those with proliferative retinopathy (now treated) and those treated previously there was no change in flow velocity.

To understand the changes of retinal blood flow in diabetic retinopathy is important because it will further our understanding of the pathophysiology of the condition and perhaps reveal processes amenable to therapy in the earliest stages of the disease. Diabetic retinopathy is now the commonest cause of blindness under the age of 65 in the United Kingdom.[1]

Retinal blood flow in diabetes will vary in response to changes in metabolic demands and may vary with the histopathological features of early retinopathy, namely generalised pericyte loss, basement membrane thickening, endothelial proliferation, and microaneurysm formation, particularly affecting the venous end of the capillary bed.[2] Flow is also affected by endothelial cell loss.

The exact effects of diabetic retinopathy on retinal blood flow are not established in spite of extensive investigations with fluorescein dye dilution techniques,[3,4] laser doppler velocimetry,[5-7] and blue field entoptoscopy.[8] This is probably due to the selection of patients and the fact that different methods measure different aspects of flow. Long-term follow-up to show changes in blood flow in large numbers of patients has not been carried out previously. In this study we report such changes in 87 diabetics and 10 normal subjects using the blue light entoptic technique.

Patients and methods

PATIENTS

Of the 126 diabetics whose retinal blood flow was measured in 1984 by the same method and described in an earlier study[8] 87 were available for reassessment two years later. Ten of the 24 healthy volunteers were also available. Of the remaining 37 diabetics eight had died, two had gone abroad, six could not repeat the test because of vitreous haemorrhage, maculopathy, or poor concentration, and 23 were either not reassessed or could not be contacted. A visual acuity of at least 6/12 was necessary to see the simulated leucocytes clearly on the TV monitor.

On entering the first study all patients had undergone a screening procedure to assess their ability to match the speed of the simulated leucocytes with the speed of their own leucocytes seen in the entoptoscope. Only those achieving reproducibility scores of at least 80% were included in this investigation.

The diabetic patients were divided into the following groups based on the level of retinopathy at the first measurement assessed ophthalmoscopically or by colour retinal photographs: (1) no retinopathy; (2) background retinopathy (from one microaneurysm only to multiple microaneurysms, haemorrhages, and hard exudates); (3) preproliferative retinopathy (as (2) plus cotton-wool spots, intraretinal microvascular abnormalities, venous abnormalities of severe degree, but no new vessels); (4) proliferative retinopathy (disc new vessels and/or new vessels

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Table 1 *Patient details at first assessment*

Retinal category	*Number*	*Mean age, years (range)*	*Mean duration of diabetes mellitus, years (range)*
Normal controls	10	32 (27–38)	–
No retinopathy	9	37 (20–51)	10 (2/52–27)
Background	24	44 (23–65)	20 (5–43)
Preproliferative	16	43 (23–53)	13 (2–30)
Proliferative	13	38 (24–58)	23 (14–42)
Photocoagulated	25	46 (19–67)	24 (2–41)

elsewhere); (5) postphotocoagulation (no new vessels remaining after argon or xenon treatment). Argon laser photocoagulation would mean at least 2000 burns of an intensity aiming at a pale grey lesion, each burn being 200–500 μm, 0·15–0·30 watt, and 0·05—0·1 second. Four of the patients had xenon treatment in addition which involved at least 150 burns of aperture 4·5 mm, power 4–15 W, and duration 1·0 second. For patients details see Table 1.

METHODS

The blue light entoptic method has been described in our earlier cross-sectional study,[8] so a brief description only will be given here. The subject matches the speed of a pattern of simulated leucocytes presented by a computer on a TV monitor with the speed of his own seen entoptically in the perifoveal capillaries when he looks into a blue light of wavelength 430 nm. The retinal speed is calculated from the TV screen speed and the subject repeats the test until three consecutive readings are obtained whose maximum deviation from the mean is less than 20%.

Table 2 *Retinal blood flow velocities at start and end of 30-month period*

Retinal category at first assessment	*Start mean mm/s (SD)*	*End mean mm/s (SD)*	*Mean duration between readings months (range)*
Normal Controls	0·57 (0·19)	0·65 (0·11)	30 (29–31)
No retinopathy	0·47 (0·22)	0·57 (0·27)	32 (24–37)
Background	0·71 (0·35)	0·48 (0·13)	33 (24–38)
Preproliferative	0·62 (0·39)	0·41 (0·14)	32 (21–39)
Proliferative	0·58 (0·26)	0·47 (0·21)	27 (21–35)
Photocoagulated	0·46 (0·14)	0·45 (0·09)	32 (23–38)

Colour photographs at the beginning and end of the study of patients in the background retinopathy group were graded by the Hammersmith Hospital system, which is based on standard photographs.[9] Photographs were graded for microaneurysms/haemorrhages and hard exudates in each of five fields. The maximum score for each of these two categories for each eye was 25.

Blood pressure, blood sugar (Beckmann glucose analyser; Clinical Instruments Division, 2500 Harbor Boulevard, Fullerton, California 92634, USA), and HbA1 levels (Corning densitometer; Corning Medical and Scientific, Corning Glass Works, Medfield, Maryland 02052, USA) were recorded each time.

Student's *t* tests (paired when appropriate) and Wilcoxon's rank sum tests were used to assess the significance of the results, p values of less than 0·05 being considered significant. Coefficients of correlation were calculated by the least squares method.

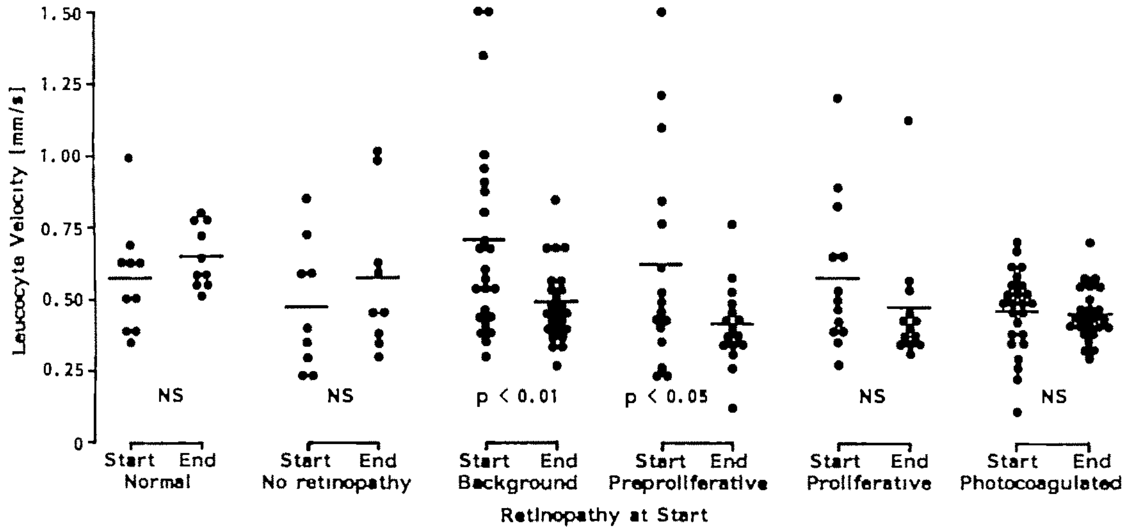

Fig. 1 *Perifoveal leucocyte velocities of diabetics and normal controls at start and end of 30-month period (NS=not significant).*

Results

There was no significant change in the retinal flow velocity of the 10 normal subjects, being 0·57 (SD 0·19) mm/s at the start and 0·65 (0·11) mm/s at the end (Table 2). The velocities of seven had increased and three decreased. The flow velocities of the diabetics with no retinopathy also showed no consistent change (0·47 (0·22) mm/s to 0·57 (0·27) mm/s), seven increasing and two decreasing. One of this group developed background retinopathy during the study and his velocity increased slightly.

Patients with background retinopathy showed a significant decrease in flow velocity from 0·71 (0·35) mm/s to 0·48 (0·13) mm/s ($p<0{\cdot}01$). The flow velocity at the end of the study was also significantly slower than that of normals at the end of the study ($p<0{\cdot}01$, Fig. 1). Their mean retinopathy grading scores for microaneurysms and haemorrhages changed from 4·83 (3·48) to 3·83 (3·43) (not significant, NS). Eight scores worsened, 12 improved, and four remained the same. The mean scores for exudates changed from 1·16 (1·34) to 1·37 (1·47) (NS). Nine scores worsened, six improved, and nine were unchanged.

The scores for microaneurysms and haemorrhages at the start of the study correlated well with those at the end of the study $r=0{\cdot}74$, $p<0{\cdot}001$ The scores for exudates at the start of the study also correlated well with those at the end of the study, $r=0{\cdot}74$, $p<0{\cdot}001$. There was no correlation between change in retinal blood flow and retinopathy, blood pressure, or HbA1.

However, six were tested before continuous subcutaneous insulin infusion (CSII) was started and at the last study had all been on CSII for at least 24 months. When these six were taken separately their flow velocity showed an insignificant change from 0·69 (0·45) mm/s to 0·57 (0·20) mm/s, whereas the flow velocity of the patients on conventional therapy fell from 0·71 (0·33) mm/s to 0·45 (0·08) mm/s ($p<0{\cdot}01$). At the end of the study the flow velocity of the patients on CSII was faster than that of patients on conventional therapy ($p<0{\cdot}05$). There was no significant change in retinopathy scores during the study in either of the above two subgroups.

Taken as a group, the patients with preproliferative retinopathy showed a decrease in flow velocity from 0·62 (0·39) mm/s to 0·41 (0·14) mm/s ($p<0{\cdot}05$). Of these 16 patients two improved to background retinopathy, in five the retinopathy remained preproliferative, two developed new vessels which remained proliferative in spite of treatment, and seven had developed new vessels which regressed completely after photocoagulation. Flow changes were not consistent with changes in retinopathy (Fig. 2).

The patients in the original proliferative retinopathy group had all undergone photocoagulation and showed an insignificant change in flow velocity from 0·58 (0·26) mm/s to 0·47 (0·21) mm/s. The mean flow velocity of the photocoagulation group was 0·46 (0·14) mm/s at the start and 0·45 (0·09) mm/s at the end, showing no change.

No significant changes were found in the levels of blood sugar, HbA1, and blood pressure, in any of the groups over the study period (Table 3). No correlation was found between leucocyte velocity and any of these parameters

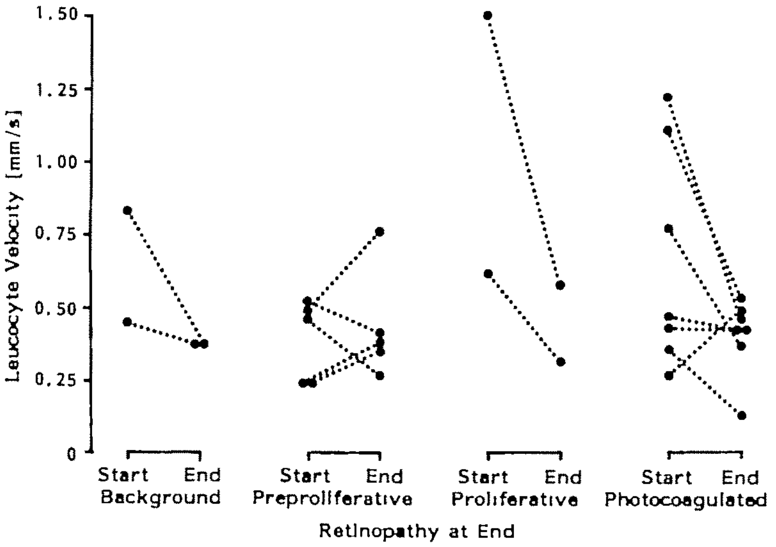

Fig. 2 *Perifoveal leucocyte velocities at start and end of 30-month period of 16 patients with preproliferative retinopathy at the start. There were no significant differences between the subgroups*

Table 3 *Blood pressure, HbA1, and blood glucose at start (S) and end (E) of 30-month period*

Retinal category at start		*HbA1 mean (SD) percentages*	*Syst BP mean (SD) (mmHg)*	*Diast BP mean (SD) (mmHg)*	*Blood glucose mean (SD) (mmol/l)*
No retinopathy	S	8·5 (1·6)	125 (9)	80 (5)	12·9 (4·1)
	E	9·2 (1·1)	118 (14)	73 (8)	13·9 (4·6)
Background	S	9·7 (1·8)	130 (19)	82 (12)	9·3 (3·8)
	E	9·6 (1·9)	138 (29)	82 (11)	11·2 (4·5)
Preprolif.	S	9·5 (1·9)	141 (21)	85 (11)	9·9 (5·1)
	E	10·2 (1·8)	136 (30)	78 (12)	9·6 (6·4)
Prolif.	S	10·9 (2·6)	136 (21)	83 (13)	11·2 (4·3)
	E	9·8 (1·0)	158 (13)	83 (8)	8·7 (5·1)
Photocoag	S	10·2 (1·8)	135 (26)	79 (9)	10·5 (6·1)
	E	10·5 (2·2)	145 (20)	78 (11)	9·8 (5·1)

Discussion

Studies on retinal blood flow in early diabetes with and without retinopathy using fluorescein dye dilution techniques showed an increase in comparison with normals.[3,4] However, this method is no longer used, as it has many shortcomings. It is invasive and measures primarily plasma flow, and even in the absence of ophthalmoscopic changes there is difficulty in assessing the volume of the vascular bed.

Laser doppler studies of retinal blood flow are based on axial velocity of red blood cells in major retinal vessels in relation to the cardiac cycle.[5-7] This is probably the best and most reproducible method available, but like the other methods it suffers from the inaccuracies caused by changes in the vessel diameter. The changes in axial velocity pulsatility in diabetes described by Feke *et al.*[8] could merely be reflecting changes in vessel wall elasticity rather than changes in true volume flow.

The blue light entoptic technique used in this study measures leucocyte velocity in the perifoveal capillaries and is subject to the same limitations in that changes in capillary diameter are unknown. This is probably important, as the macular capillary diameter is smaller than that of leucocytes, which in addition are the least deformable component of blood. The method is also the most subjective but has been shown to be reproducible in practice.[8]

Patients in the background retinopathy group showed a decrease in retinal flow velocity over the 30-month period, and at the end of the study their flow velocity was also significantly slower than that of normals. In diabetes the factors tending to increase blood flow are the increased metabolic rate[10] and the autoregulatory stimulus of any hypoxia if present,[11,12] and acute hyperglycaemia,[13] though the last has not been confirmed in humans.[14] The flow would be reduced by a decrease in red cell deformability[15-17] and an increase in red cell aggregation[18] and blood viscosity,[19] none of which were measured in this study. Reduction of flow velocity would also be expected if the retinopathy deteriorated, since flow is significantly reduced in patients with large areas of capillary non-perfusion.[8]

This study failed to show worsening of retinopathy on clinical examination or in colour photographs. Fluorescein angiograms were not done on enough patients, and especially not in the retinal periphery, to allow comment on increasing non-perfusion. However, the results of this study, showing a blood flow velocity slower than that of normals, are in line with those of laser doppler velocimetry studies[7] which showed reduced red cell velocity at all stages of retinopathy even though volume flow was found to be reduced only in photocoagulated patients.

The flow velocity of the patients on CSII showed an insignificant reduction, whereas that of patients on conventional diabetic therapy fell significantly. This finding supports the view that the ongoing effects of diabetes, which are apparently tending to reduce flow velocity, are less marked in patients on CSII.

The results of the 16 preproliferative patients are even more difficult to explain. While reduction in flow was expected and seen in those who were photocoagulated or developed proliferative retinopathy, it was unexpected in the two patients who improved and reverted to background retinopathy (Fig. 2). It is possible that blood flow is more variable in these patients, but we have not found a reason for this.

The retinal flow velocities of the photocoagulated patients, including those in the original proliferative group who were photocoagulated after the first measurement, were unchanged over the period of the study. This may indicate that the flow was already adjusted to the reduced metabolic demands of the smaller area of viable retinal tissue, or that the vessels were already so damaged that change in flow was impossible, or that perifoveal flow was preserved at the expense of flow to more peripheral areas in the face of further capillary closure. Changes up to 20% could be missed owing to the sensitivity of the method. It will be observed from Fig. 1 that the significant shifts in flow rate seem to be due to loss of outlying higher values rather than a general overall shift. This may be explained by the change in size of the simulated leucocytes on the TV screen from 4 pixels to 1 pixel between the start and end of the study. This change, which was the result of an irreversible modification to allow greater flexibility in other respects, may have affected the performance of some patients more than others. The smaller spread of values at the end of the study in five out of six groups would suggest that this system was more reliable.

In conclusion, over a 30-month period retinal blood flow velocity was reduced in diabetics with background retinopathy but remained unchanged in those with normal fundi and those who had undergone photocoagulation previously. This would suggest that, in the presence of background retinopathy, longer duration of diabetes and possibly reduced viable retinal tissue both tend to reduce flow.

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Epithelial downgrowth: a 30-year clinicopathological review

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SUMMARY We performed a retrospective clinicopathological review of 124 patients with epithelial downgrowth seen over a 30-year-period at the Massachusetts Eye and Ear Infirmary. The purpose of this study was to determine predisposing factors in the development of epithelial downgrowth, diagnostic symptoms and signs, and the results of various types of treatments. The incidence of this condition after cataract surgery was 0·12%, decreasing to 0·08% over the latter decade. 82% of postsurgical patients with epithelial downgrowth presented to the ophthalmologist within one year following surgery, commonly complaining of decreasing visual acuity, red eye, and pain. The most common presenting signs of epithelial downgrowth were retrocorneal membrane, which was seen in 45% of patients, glaucoma in 43%, corneal oedema in 21%, and a positive Seidel test in 23%. We found that a variety of conditions predispose to epithelial downgrowth but that no one factor was present in all cases. Damage to the underlying endothelium, corneal stromal vascularisation, and stromal downgrowth appeared to be important events not emphasised in prior studies. The angle was partially or totally closed in 87% of enucleation specimens. Patients treated surgically underwent fewer enucleations than those treated medically or not treated.

Epithelial downgrowth is a serious though relatively uncommon complication of ocular surgery and trauma which frequently results in blindness from intractable glaucoma. In the older literature 17–26% of all enucleations after cataract surgery are reported to be due to this complication.[1-7] Treatment of it has met with little success despite attempts with a variety of methods.

We reviewed all cases of epithelial downgrowth histologically diagnosed in the David G Cogan Eye Pathology Laboratory at the Massachusetts Eye and Ear Infirmary (MEEI) over a 30-year period. The object of this study was to re-evaluate and update the known predisposing factors in the development of epithelial downgrowth, diagnostic symptoms and signs, and the results of various types of treatments.

Materials and methods

One hundred thirty-nine cases of epithelial downgrowth recorded in the files of the David G Cogan Eye Pathology Laboratory at the MEEI from January 1953 to May 1983 were reviewed, and pathological specimens were examined to confirm the diagnosis. The specimens examined histopathologically are listed in Table 1. Fifteen cases diagnosed clinically to have epithelial downgrowth could not be confirmed histologically from available slides and were excluded.

The medical records of all histologically confirmed cases were reviewed. The patient's age, sex, type of surgical procedure or trauma, length of time before clinical presentation, presenting signs and symptoms, concurrent illnesses, medications, and visual acuity at the time of enucleation were recorded. The operative notes of patients who had undergone surgery were reviewed for type and number of sutures, presence and type of conjunctival flap, and operative complications. The patients' ophthalmologists were contacted for clinical findings on follow-up visits. Details of various modes of therapy used in the treatment of epithelial downgrowth, as well as the results and the amount of follow-up, were compiled.

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Table 1 *Specimen type used to confirm diagnosis of epithelial downgrowth*

Specimen type	*Surgical patients*	*% of eyes*	*Trauma patients*	*% of eyes*
Corneal button alone	28	26	2	11
Iridectomy alone	21	20	0	0
Iridectomy followed by enucleation*	6	6	1	6
Enucleation alone	33	31	13	72
Anterior champer tap alone	10	9	2	11
Anterior chamber tap followed by enucleation*	2	2	0	0
Iridectomy and corneal button*	4	4	0	0
Iridectomy and anterior chamber tap*	2	0	0	0
Total	120	100	19	100

*Counted as two specimens in total.

Table 2 *Surgical procedures preceding epithelial downgrowth*

Surgery	*Number of eyes*	*%*
Intracapsular cataract extraction	76	72
Planned extracapsular cataract extraction	9	8
Unplanned extracapsular cataract extraction	6	6
Penetrating keratoplasty	13	12
Pterygium excision	1	1
Aspiration of aqueous	1	1
Total	106*	100

*Includes two patients with bilateral epithelial downgrowth.

The pathological specimens were reviewed and evaluated for: appearance and organisation of the epithelium, location and extent of downgrowth, and the presence of an unclosed wound or fistula, incarcerated tissue, stromal vascularisation, or synechiae. The presence of partial or complete angle closure and the depth of the anterior chamber were recorded as well.

Results

One hundred twenty-four histopathologically confirmed cases of epithelial invasion of the anterior chamber were seen at the MEEI between January 1953 and May 1983. Of these, 106 followed surgical procedures and 18 ocular trauma. Table 2 details the surgical procedures which preceded epithelial downgrowth.

EPIDEMIOLOGY

The ratio of males to females was 1:1·7 in the surgical group and 3·5:1 in the trauma group. The age at the time of surgery ranged from 3 to 89 years. Sixty-eight of the 106 surgical patients were over the age of 60. In contrast, the post-trauma patients ranged from 10 to 58 years of age at the time of trauma, with a mean of 26 years. Although there was approximately equal involvement of the right and left eye in the surgical group (54 vs 52), the right eye was twice as frequently involved in the trauma group (12 vs 6).

A total of 44 496 cataract extractions were performed at the MEEI between January 1953 and May 1983, 22 272 of which were completed between January 1973 and May 1983. Fifty-four of the patients with epithelial downgrowth after cataract extraction over the entire 30-year period and 17 over the last decade were operated on at the MEEI. Thus the minimum incidence of epithelial downgrowth after cataract extraction at the MEEI over the entire 30-year period was 0·12%, dropping to 0·076% in the last decade. 75% of patients presented to the clinician with epithelial downgrowth within the first six postoperative months, with a mean of five months (Fig. 1).

CLINICAL REVIEW

Of the surgical cases 11% were noted to have operative complications at or immediately following surgery. Of these, 50% had vitreous loss. Persistent hypotony, lens capsule rupture, inadvertent filtering bleb, and anterior chamber haemorrhage were also reported. Of those who had epithelial downgrowth following cataract extraction conjunctival flaps were limbal based in 16% and fornix based in 52%. In 32% the data were not available. The fornix based flap was most commonly used at MEEI; however, the exact number of limbus vs fornix based flaps during this 30-year period was not obtainable.

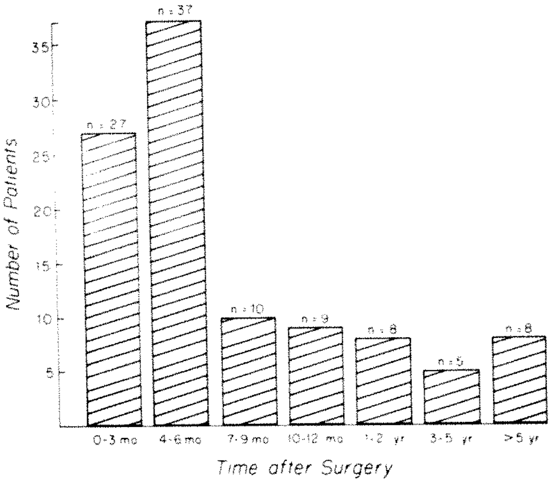

Fig. 1 *Time to presentation with epithelial downgrowth after ocular surgery.*

Table 3 *Presenting chief complaint in patients with epithelial downgrowth*

Symptom	*Surgical patients*	%	*Trauma patients*	%
Decreasing visual acuity	35	34	6	33
Red eye	19	18	2	11
Pain (without glaucoma)	14	13	7	39
Tearing	6	6	0	0
Photophobia	2	2	2	11
Foreign body sensation	2	2	1	6
Flashes of light	1	1	0	0
No symptoms recorded	25	24	0	0
Total	104	100	18	100

Five of the postsurgical patients were taking anticoagulants for phlebitis and pulmonary embolism. No other medication was identified as affecting the development of epithelial downgrowth.

Visual acuity at the time of enucleation was less than 20/200 in all cases. The reason for enucleation of eyes was painful glaucoma in a blind eye in the majority of patients. The presenting chief complaints from patients with epithelial downgrowth are itemised in Table 3, while the presenting signs are detailed in Table 4.

PATHOLOGY

Epithelial downgrowth was most often found in the form of sheets of cells, less commonly in cysts or as scattered islands of cells. All enucleations were of eyes with epithelial downgrowth in the form of sheets alone or sheets and cysts. In 17 of the postsurgical specimens surface epithelium extended through the wound and into the anterior chamber. The most typical finding consisted of one to three layers of stratified non-keratinised squamous epithelium of conjunctival or corneal origin extending over the posterior cornea and on to the anterior iris (Figs. 2, 3). Unfortunately the source of the epithelium could not be certainly identified in the majority of the specimens because of limited tissue for further

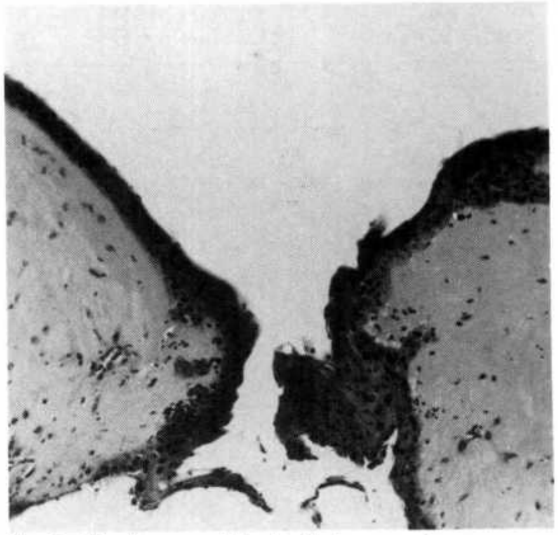

Fig. 2 *Fistulous wound lined with downgrowing epithelium. H and E, ×60.*

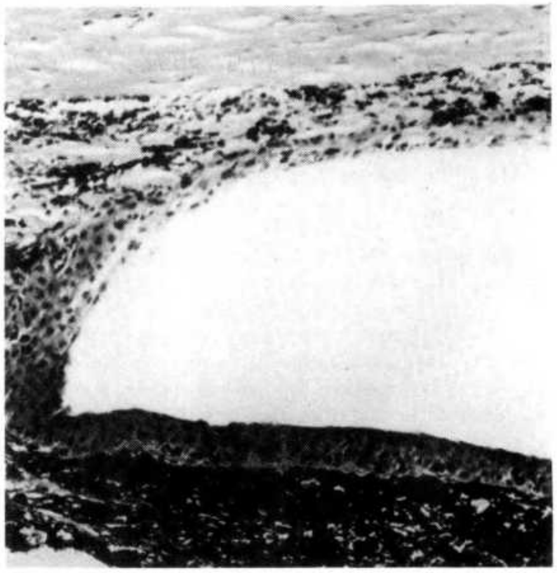

Fig. 3 *Epithelium growing on posterior surface of cornea, across the angle, and on to the anterior surface of the iris. H and E, ×65.*

Table 4 *Presenting signs in patients with epithelial downgrowth**

Sign	*Surgical patients*	%	*Trauma patients*	%
Retrocorneal membrane	48	46	1	6
Painful glaucoma	32	31	4	22
Positive Seidel test	24	23	1	6
Corneal oedema	22	21	4	22
Hypotony	17	16	4	22
Painless glaucoma	14	13	1	6
Iritis	11	11	1	6
Pupillary distortion	10	10	2	11
Iris cyst	8	8	1	6
Anterior chamber cyst	8	8	6	33
Discharge	5	5	1	6
Band keratopathy	5	5	3	17
Bullous keratopathy	3	3	0	0
Flat anterior chamber	2	2	0	0
Iris whitening on photocoagulation	2	2	0	0
Retinal detachment	1	1	1	6
Vitreous haze	1	1	0	0

*Many patients had more than one sign of epithelial downgrowth.

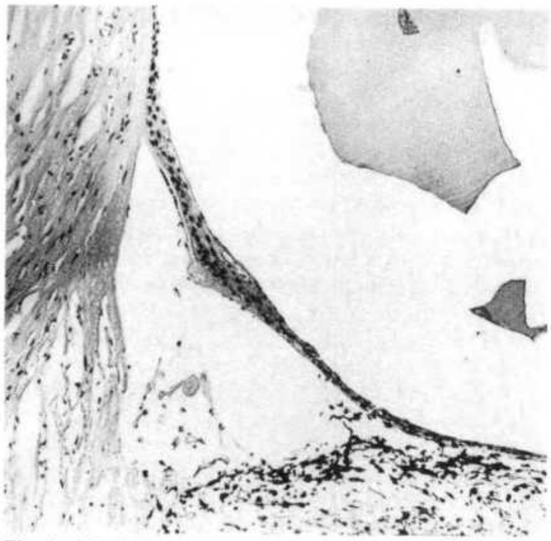

Fig. 4 *Epithelium growing across the angle. H and E, ×57.*

studies. Obstruction of the trabecular meshwork was noted in several cases (Fig. 4). Table 5 lists the findings in corneal button and enucleation specimens.

TREATMENT

We recorded the course of 75% of the postsurgical patients for a three-year period. 62% of these patients were treated surgically, 11% were treated medically, and the remainder had no therapy. Surgical treatments included excision of downgrowth, iridectomy, cryotherapy, cautery, vitrectomy, penetrating keratoplasty, cyst aspiration, and photocoagulation. Medical treatments included radiation therapy, alcohol and potassium chloride swabbing, steroids, and antibiotics. Many of the patients were treated with more than one mode of therapy. 63% of the surgically treated eyes had excision of the downgrowth, and 50% of those eyes also had an iridectomy. Penetrating keratoplasty was performed in 29% of surgically treated eyes. In most cases medical therapy consisted of topical and systemic steroids and antibiotics.

Table 5 *Findings in corneal button and enucleation specimens*

Finding	*Surgical patients*	*% of specimens*	*Trauma patients*	*% of specimens*
Fistula	19	26	9	56
Stromal vascularisation	65	89	15	94
Stromal downgrowth	40	55	6	38
Shallow anterior chamber*	37	90	10	71
Normal anterior chamber*	4	10	4	29
Peripheral anterior synechiae	52	71	12	75
Incarcerated iris	11	15	4	25
Incarcerated lens capsule	2	3	1	6
Open angle*	4	10	3	21
Closed angle*	37	90	11	79
Foreign body	0	0	1	6

*Determined only in enucleated specimens.

Of the post-surgical patients 52% eventually underwent enucleation. Only 19% of patients treated with surgical excision and iridectomy resulted in enucleation. 21% of patients treated with penetrating keratoplasty had enucleations. All patients treated medically and 95% of those with no therapy indicated in the chart had enucleations.

Discussion

Epithelial invasion of the anterior chamber has been reported most frequently after cataract surgery and ocular trauma, though its occurrence after penetrating keratoplasty,[8-10] pterygium removal, aspiration of aqueous, and passage of a transcorneal (McCannel) suture[11] has been noted. This study confirms the results of earlier reports with 86% of our cases occurring after cataract extraction and 12% after penetrating keratoplasty.

The incidence of reported cases of epithelial downgrowth following surgical procedures over the 30-year study period at MEEI was calculated to be 0·12%, decreasing to 0·076% over the latter decade. This trend confirms an earlier but smaller study by Christensen, who observed a decrease over a 20-year period at the University of Oregon.[7] The decrease in the rate of occurrence may be due to improved surgical technique with the development of microsurgical instrumentation and improved suture material resulting in better wound closure.

A fistulous wound may predispose to epithelial downgrowth by facilitating egress of epithelial tissue. In corneal button and enucleation specimens we found that only 18% of the postsurgical patients had incarceration of iris or lens capsule in the wound. However, fistulous wounds were present in 26% of postsurgical patients and 56% of post-trauma patients. As might be expected, a higher incidence of uveal tissue was noted intracorneally after trauma than after surgery. Our results contrast with an earlier study by Allen and Duehr,[12] who found incarceration in 17 of 20 postsurgical patients. We saw several examples of invading epithelium in suture tracks consistent with those described by Dunnington and Regan.[13]

The biochemical and physical substrate necessary for epithelial growth in the anterior chamber has been debated by previous investigators. Experimental studies have shown that aqueous alone cannot support the growth of epithelium.[14] While we found that cellular growth on the anterior iris was more luxuriant than on the posterior cornea, averaging three to five cell layers in thickness, in 19% of our postsurgical cases, there was no epithelial downgrowth on the iris.

Stromal vascularisation was seen in 89% of the corneal and enucleation specimens from postsurgical patients and in 94% of the trauma patients. Several eyes had areas of stromal vascularisation up to 6 mm from the wound, but the majority of blood vessels were situated along the tract of the wound. We suggest that stromal vascularisation appears to be an important source of nutrition for the downgrowing epithelium. The influence of the vascularity of the substrate on which epithelium grows has been previously noted by Cogan.[15]

While wound fistula and stromal vascularisation are thought to promote epithelial downgrowth, experimental evidence suggests that the presence of endothelium inhibits epithelial growth in organ culture through direct intercellular interactions.[16] Fry[17] had observed an absence of marked degeneration of corneal endothelial cells in six cases of epithelial downgrowth, even in places where the endothelium was not covered by invading epithelium. Our study has shown attenuation or disruption of endothelium in most cases in which the epithelium has migrated to the posterior cornea, supporting the conclusions of Cameron *et al.*[14] We could not determine whether the endothelial disruption preceded or resulted from the epithelial downgrowth.

Dunnington[18] believed that the use of corneoscleral sutures in cataract extraction was responsible for a higher incidence of epithelial downgrowth. However, Allen and Duehr[12] reviewed 5246 cataract operations and found that multiple corneoscleral sutures did not increase the incidence of downgrowth. We found that efficient closure of the incision with improved surgical technique and instrumentation appears to decrease the incidence of epithelial downgrowth, while the number of sutures used did not appear to be an important factor.

We made note of the type of suture material used during surgery to determine whether this was a risk factor. Dunnington and Regan[19] noted rapid proliferation of epithelium along the track of silk suture but not along surgical gut. In another study Dunnington and Regan[22] stated that epithelial downgrowth was produced when silk sutures were used, but could not be produced with surgical gut. Our data show no difference in the incidence of downgrowth after the use of either suture type. This is somewhat surprising when one reasons that silk favours epithelial growth along its track because it does not swell and mechanically inhibit epithelium. It is also interesting to note that more recent suture materials such as nylon, Vicryl, and Dexon also had several cases of epithelial downgrowth postoperatively.

There appears to be no single mechanism responsible for the glaucoma seen in many of our patients. Obstruction of the trabecular meshwork by epithelium was noted (Fig. 4). This may be an important mechanism for the development of glaucoma.[20] Histological examination of all the corneal buttons and enucleated eyes revealed the presence of synechiae in 73%, a shallow anterior angle in 80%, and a totally closed angle in 85%. Chandler and Grant [21] suggest pupillary block as another cause of glaucoma.

Stromal downgrowth, defined in our study as a collagenous proliferation on the posterior cornea, was seen in 55% of surgical patients and 38% of trauma patients. Stromal downgrowth has been previously reported after trauma[22] and surgery.[7 19 23] Allen[5] found 36% of eyes enucleated after cataract extraction had stromal downgrowth and similar findings were reported by Dunnington.[23] To our knowledge there are no previous reports of the presence of stromal downgrowth in cases of epithelial downgrowth. Our results indicate that, although stromal downgrowth occurs more commonly than does epithelial downgrowth following surgery or trauma,[5] it is associated with epithelial downgrowth in only 38 to 55% of cases.

The source of epithelium for downgrowth is probably conjunctival in most cases While we were often unable to differentiate conjunctival from corneal epithelium, none of the patients who underwent a planned or unplanned extracapsular cataract extraction showed evidence of lens epithelial migration. We consider it is highly unlikely that lens epithelium is a source of epithelium for downgrowth.

Epithelialisation of the anterior chamber can occur in the form of sheets or cysts; individual cells seen on anterior chamber taps have separated from sheets or cysts. 93% of surgical cases and 78% of traumatic cases had at least some epithelial downgrowth in the form of sheets When analysing enucleated eyes we found that all enucleations had epithelial downgrowth in the form of sheets. This confirms the belief that patients with cysts tend to have a better prognosis[24] or respond to treatment more favourably than do patients who have sheets of epithelial downgrowth.

Binder and Binder[25] and Bick[26] found that when the prothrombin levels was less than 30% of normal there was inhibition of early fibroblast formation, allowing the epithelium to grow freely down the wound and into the anterior chamber. Five of our postsurgical patients were anticoagulated for phelbitis and pulmonary embolism, raising the possibility that anticoagulants may adversely affect epithelial downgrowth patients. No other medication was identified as affecting the development of epithelial downgrowth.

Various surgical and medical techniques have been devised for treatment of epithelial downgrowth.[27–32] Despite extensive attempts by many investigators the prognosis even with treatment remains bleak, most eyes having a visual acuity of 20/200 or worse postoperatively.[29,30] Our study confirms the poor prognosis in this disease, though it does suggest that treatment improves outcome in some cases. No single method of treating the epithelial downgrowth could be singled out as being the most effective. However, those eyes treated with at least some surgical technique fared better than those treated by antibiotics or steroids alone. The latter group had enucleated eyes in eight out of 10 cases. Admittedly this better outcome may reflect biased case selection for operative intervention Some of the patients treated by surgical procedures developed postoperative complications including glaucoma, corneal oedema, and hypotension, though it is not clear how many resulted from the presence of intraocular epithelium as opposed to the surgical treatment. Other authors have also reported complications such as vitreous haze, retinal detachment, ciliary body detachment, hyphaema, vitreous haemorrhage, and a residual fistula. A recently developed animal model confirms that destruction of all invading epithelium is difficult.[33] Perhaps new therapeutic methods employing antimetabolites together with surgical intervention will prove effective in halting, if not eradicating, this disease process.

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Mesectodermal leiomyoma of the ciliary body: case report

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SUMMARY The clinical, light microscopical, and electron microscopical features of a mesectodermal leiomyoma of the ciliary body are presented. This exceptionally rare and apparently benign tumour is considered to be of neural crest origin. In the case described the tumour cells were seen to contain thin filaments with focal densities and conspicuous numbers of mitochondria, and smooth muscle protein was demonstrated by immunohistochemical means.

Smooth muscle tumours of the ciliary body are extremely rare. In 1977 and 1978 Jakobiec *et al.* reported three cases of an unusual 'hybrid' smooth muscle and neuroectodermal tumour of the ciliary body.[1 2] They proposed that the unusual neural appearance of this smooth muscle tumour reflected its origin from the neural crest cells that contribute to the formation of bone, cartilage, connective tissue, and smooth muscle in the head and neck region. These neural crest derived tissues have been termed 'mesectoderm', and hence the terminology of Jakobiec *et al.* for the ciliary body tumour—a mesectodermal leiomyoma. The present report concerns a fourth example of this highly unusual tumour and highlights some histopathological differences from the previously published cases.

Case report

HISTORY AND CLINICAL COURSE

A previously fit 38-year-old male teacher was noticed to have an apparent iris tumour on routine visit to an optician. Corrected visual acuity was 6/12 right eye, 6/5 left eye. On closer inspection the tumour was seen to be whitish, with overlying blood vessels, and appeared to be located within the ciliary body at 5 to 6 o'clock with some displacement of the iris root adjacent to its anterior edge (Fig. 1). The tumour did not invade the angle but pushed against the lens. There was no cataract and the intraocular pressure was normal. Fundus examination after full mydriasis showed a rather more pigmented, ciliary body tumour but no serous retinal detachment. The left eye was normal. An ultrasound examination of the right eye was suggestive of a malignant melanoma of the ciliary body, but the overall clinical appearance was atypical of this tumour. General physical examination and laboratory investigations were normal.

In December 1986, four months after the tumour was first noticed, the patient underwent an iridocyclectomy, with excision of a clear margin of normal ciliary body and iris surrounding the tumour. The postoperative course was uneventful and the patient had 6/12 vision five months after surgery.

PATHOLOGY

The specimen was received in formalin fixative and consisted of a sector of the ciliary body which contained a firm ovoid and whitish tumour measuring 8×7×5 mm.

Light microscopy. Low power examination of haematoxylin and eosin stained sections revealed a well circumscribed tumour of the ciliary body which was situated where the normal ciliary muscle would have been (Fig. 2). It was covered on one surface by the pigmented and non-pigmented ciliary epithelium and blended with normal ciliary muscle on another surface. The tumour consisted of sheets of polygonal

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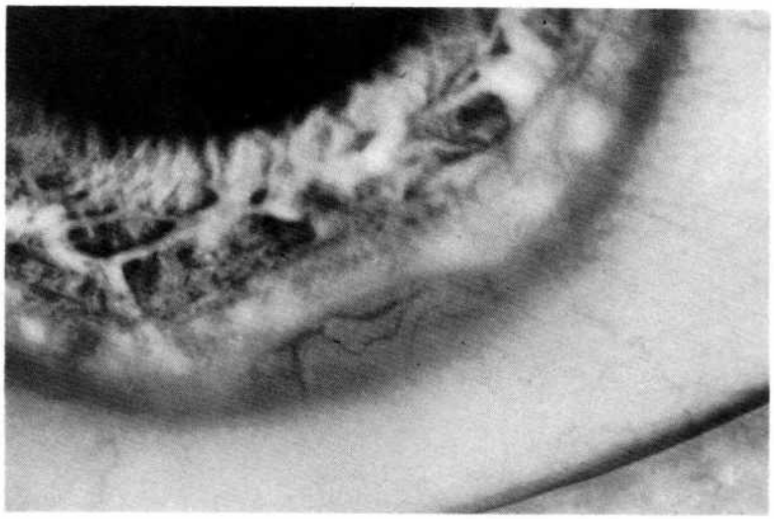

Fig. 1 *Clinical photograph of patient's right eye showing vascularised, whitish tumour impinging on and displacing the inferior iris.*

cells which tended to become fusiform at the periphery (Fig. 3). The nuclei were central, often with prominent nucleoli, but there were no mitoses. The cytoplasm was abundant and eosinophilic, and whereas in some areas it had an irregular hyaline appearance, in others it appeared more fibrillary (Fig. 4). Large numbers of mast cells were scattered throughout the tumour. There was no staining of the tumour cells by the periodic acid-Schiff (PAS) technique, although PAS positive material was present around many cells. Reticulin staining outlined many cells individually (Fig. 5a). Phosphotungstic acid-haematoxylin (PTAH) and Masson-trichrome stains revealed a few longitudinally orientated fibrils within the more peripherally placed spindle cells. A Fontana-Masson stain for melanin was negative within the tumour. Azure-A staining highlighted the numerous mast cells (Fig. 5b).

Immunohistochemistry. Staining for cytokeratin, glial fibrillary acidic protein (GFAP), S100 protein, and desmin was carried out by a standard three-stage immunoperoxidase technique. There was no staining for cytokeratin and GFAP. Staining for S100 protein was present in the overlying neuroepithelium and melanocytes trapped within the ciliary muscle, but was absent within the tumour. Antiserum against desmin reacted positively with both the normal ciliary muscle and the tumour cells.

Transmission electron microscopy. Low power magnification revealed angular and polygonal cells, many with blunt, irregular processes (Fig. 6a). Blood vessels were scanty, but numerous mast cells were

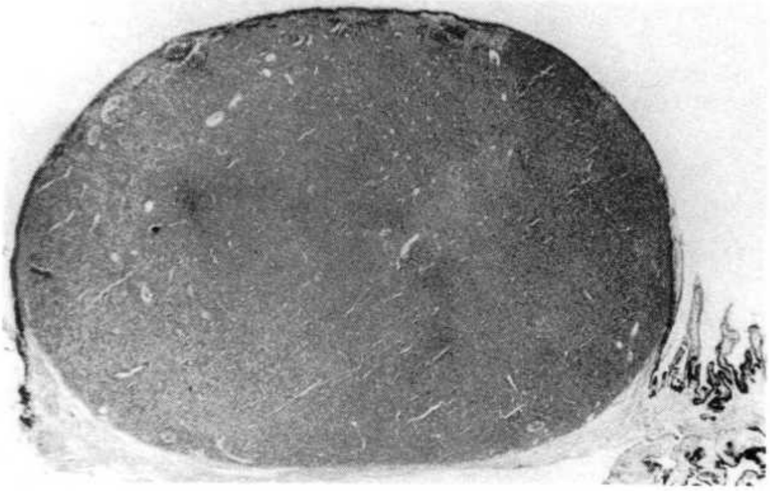

Fig. 2 *Low power photomicrograph to show placement of tumour where normal ciliary muscle would have been. It is covered by normal ciliary epithelium and blends into the surrounding ciliary smooth muscle. H and E, ×15·5.*

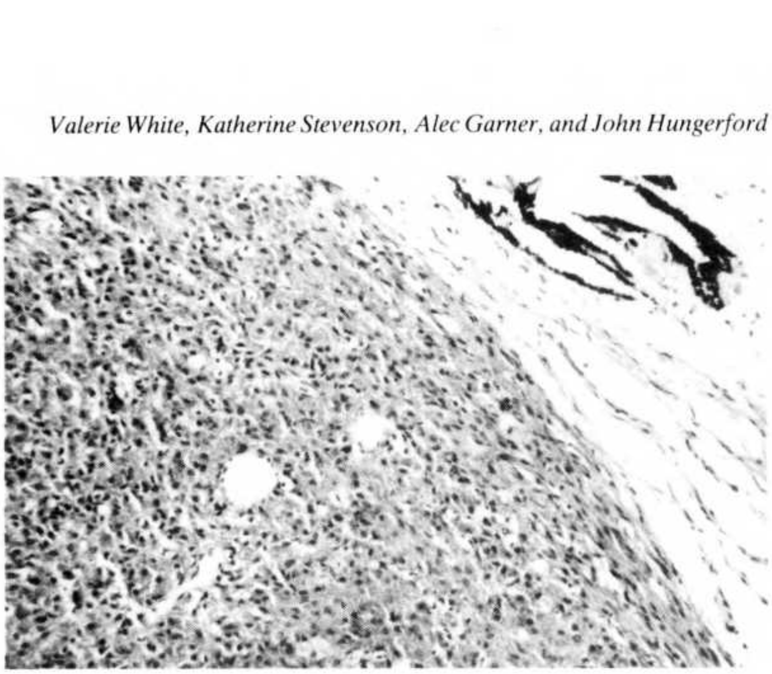

Fig. 3 *Cells of the tumour are polygonal centrally, but tending to become fusiform at the periphery. H and E, ×120.*

visible. Nuclei were pale with small clumps of heterochromatin and prominent nucleoli (Fig. 6b). The cytoplasm was about equally filled with abundant mitochondria and longitudinally placed thin filaments (Fig. 6c). The mitochondria were often densely packed and abnormally shaped, with occasional tubular forms (Figs. 7a and b), while the thin filaments measured 4–8 nm in diameter and contained irregularly placed focal densities (Fig. 7c). Only occasional Golgi bodies and endoplasmic reticulum were present. One cilium was seen. Each cell was surrounded by an external lamina which was focally interrupted and focally duplicated. Occasional poorly formed junctions were present (Fig.

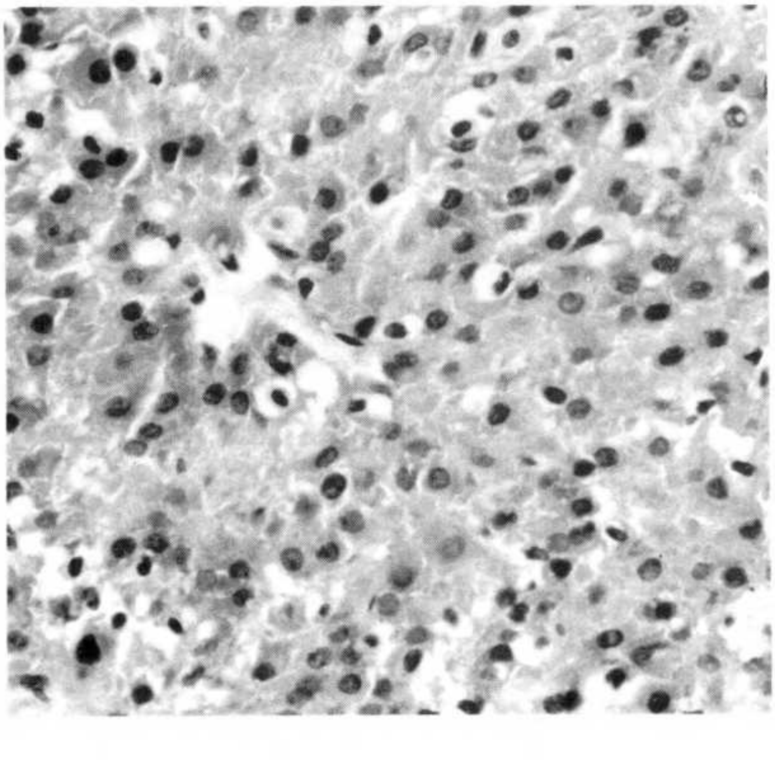

Fig. 4 *The nuclei are round, often with prominent nucleoli. Cytoplasm is abundant, eosinophilic and hyaline in some areas, while fibrillary in others. H and E, ×450).*

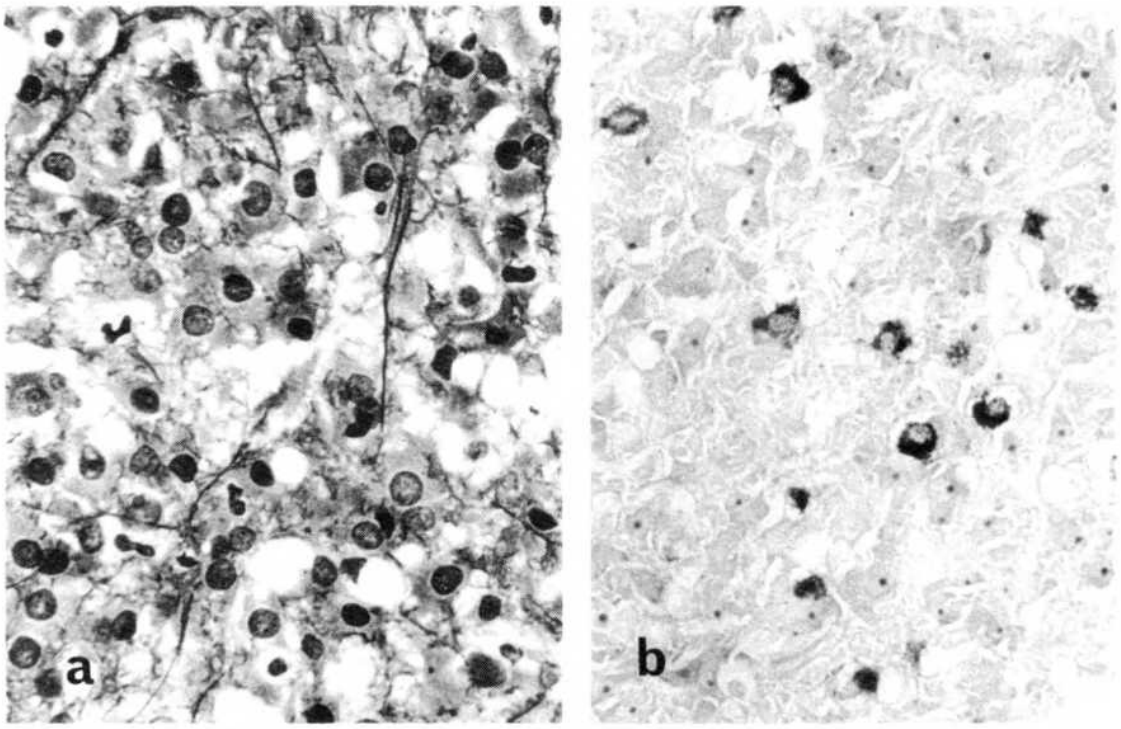

Fig. 5 a: *Reticulin outlining of individual cells. Reticulin stain,* ×*450.* b: *Large numbers of mast cells are scattered throughout the tumour. Azure-A,* ×*450).*

6d). No melanosomes, neurotubules, neuronal wrappings, dense core granules, well-formed desmosomes, or pinocytotic vesicles were seen.

Discussion

Light microscopic differential diagnosis of this unusual tumour included epithelioid leiomyoma, amelanotic naevus or well differentiated melanoma, peripheral nerve tumour, paraganglioma or haemangiopericytoma. The diagnosis of a type of leiomyoma was supported by the electron microscopic demonstration of thin filaments with focal densities and the merging of the tumour with the normal musculature of the ciliary body. The demonstration of desmin by immunohistochemistry constituted further evidence of a muscle tumour. The conspicuously numerous mitochondria raised the possibility of an oncocytoma, but this was not considered to be substantiated either by the position of the tumour below the ciliary epithelium, within the ciliary muscle, or by the lack of epithelial features such as tight junctions and well formed desmosomes on electron microscopy.

In 1977 Jakobiec *et al.* described two cases of an unusual tumour of the ciliary body which they termed a mesectodermal leiomyoma.[1] The light microscopic appearances of their cases had led them to think that they were neural tumours, in one case of glial or ganglionic origin and in the other case of peripheral nerve origin. On electron microscopy they found thin cytoplasmic filaments with focal fusiform densities and focal and multilaminated external lamina, features of smooth muscle differentiation.[3] The fibrillary appearance was given by tangled cell processes containing thin filaments with focal densities. They postulated that these 'hybrid' smooth muscle and neural tumours could develop owing to the origin of most of the ocular and periocular supporting tissues from the neural crest.[4] Experiments in birds have revealed that only the external ocular muscles and vascular endothelia arise from true mesoderm, while most of the other so called 'mesodermal' tissues, including the smooth muscle of the ciliary body, arise from the neural crest.[5] In 1978 Jakobiec and Iwamoto reported a similar tumour of the ciliary body which was associated with a naevus, further evidence of a neural crest origin.[2] A case of presumed mesectodermal leiomyosarcoma of the antrum which invaded the orbit has also been reported.[6]

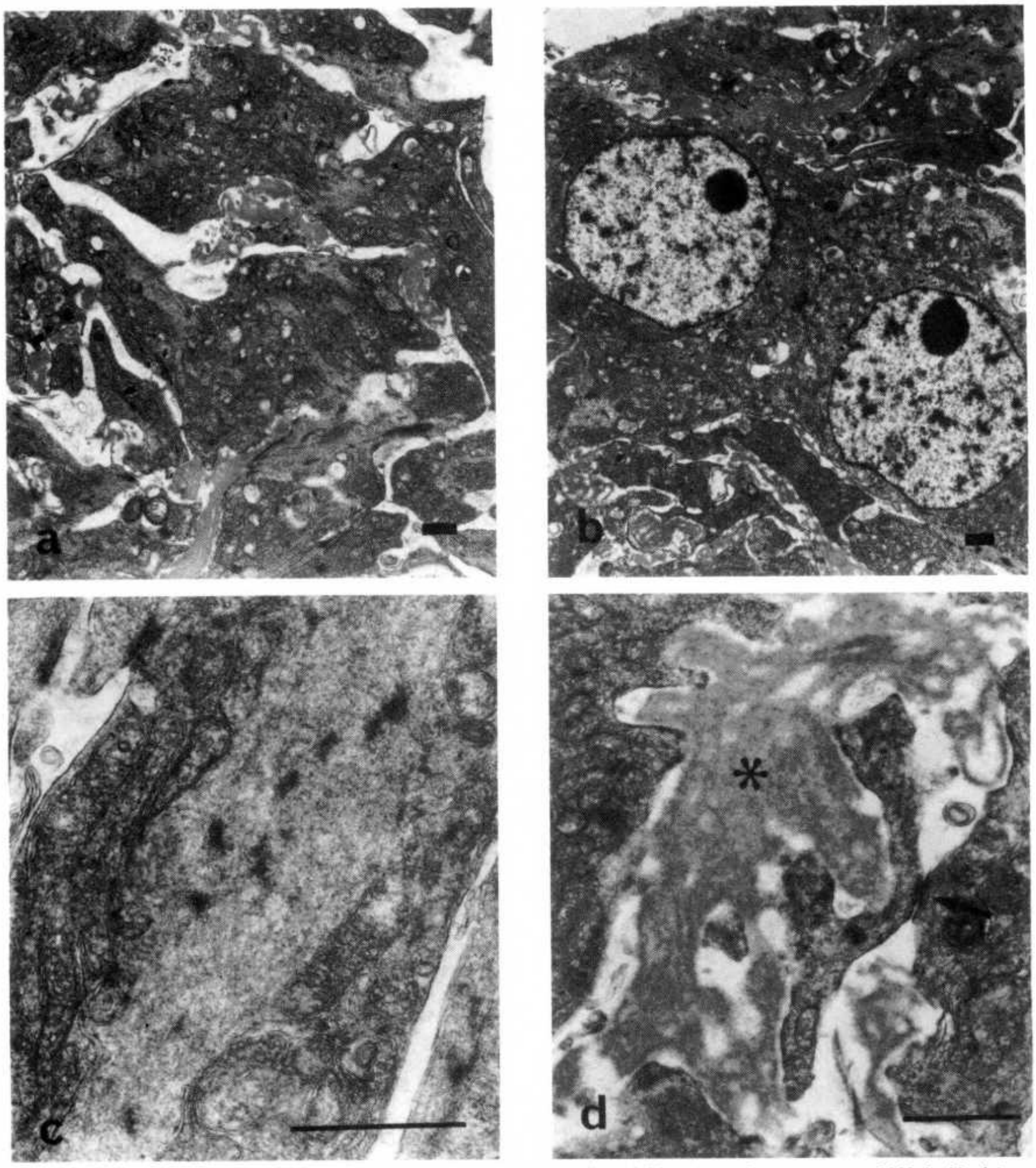

Fig. 6 a: *Low magnification electron micrograph to show angular cells with blunt irregular processes.* ×*5000.* b: *Nuclei are round and pale with prominent nucleoli.* ×*4000.* c: *Cytoplasm is about equally filled with thin filaments and mitochondria.* ×*25 000.* d: *Focally duplicated external lamina (asterisk), and poorly formed junctions are present (arrow).* ×*17 000. Bar markers=1·0* μ*m.*

The light microscopic appearance of the present case is not suggestive of a tumour of neural origin, and the most prominent feature is the many abnormal mitochondria. Although Jakobiec *et al.* in their second case comment on numerous degenerated mitochondria, they do not display many in the published electron micrograph.[1] Oncocytic cells in the thyroid, which are distinguished by a cytoplasm

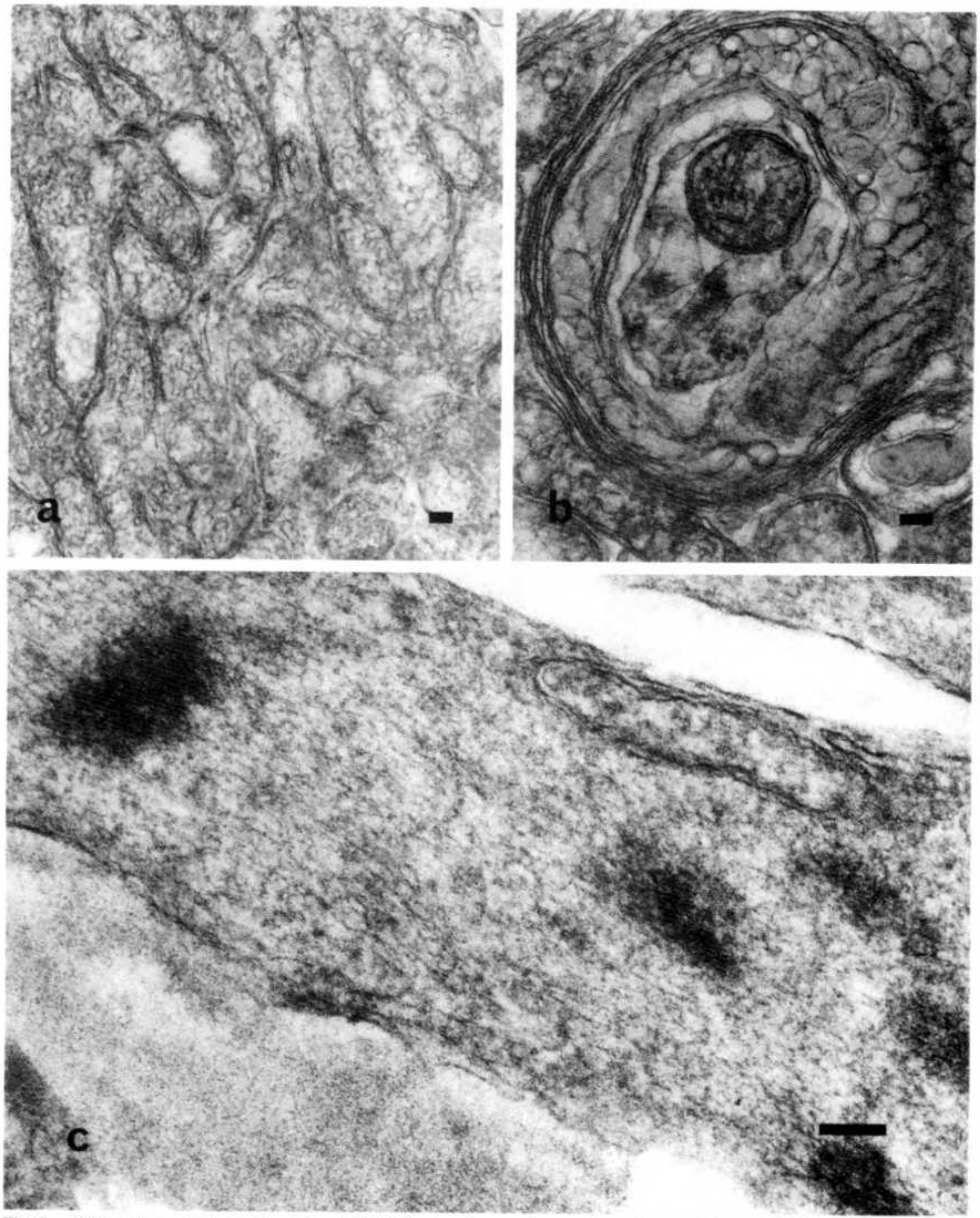

Fig. 7 a: *Densely packed mitochondria. ×34 000.* b: *An abnormal appearing mitochondrion. ×50 000.* c: *Cell process containing thin filaments with scattered focal densities. ×100 000. Bar markers=0·1 μm.*

full of mitochondria, have been shown to contain increased amounts of the oxidative enzymes isocitrate dehydrogenase, succinate dehydrogenase, and cytochrome oxidase, and are thought to reflect organelle hyperplasia in the face of decreased cellular function.[7] Whether this increase in oxidative enzymes occurs in smooth muscle cells is unknown.

The similarities between the present case and those previously reported override the differences and include the round pale nuclei with prominent nucleoli, eosinophilic fibrillary background, blending of the tumour into the normal ciliary muscle, numerous mast cells, cytoplasmic fibrils on PTAH staining, reticulin outlining of single cells, and the thin cytoplasmic filaments with focal densities seen on electron microscopy. Micropinocytotic vesicles, a usual feature of smooth muscle cells, may be absent as in this case, and depend on the physiological state of the cell.[3]

Meyer *et al.* published the first case of a spindle cell leiomyoma of the ciliary body to be studied by electron microscopy.[8] Light microscopic findings were characteristic of leiomyomas seen elsewhere in the body. Electron microscopy showed bundles of thin filaments with focal densities orientated along the long axis of the cells, micropinocytotic vesicles, and external laminae. Smooth muscle tumours occurring in other ocular sites have been reported in the choroid[9] and the orbit,[10-12] with electron microscopic verification. Although according to Green no leiomyomas of the iris have been reported including electron microscopic studies,[13] there is reason to believe that they occur.[14]

The present tumour was thought to be benign on light microscopic appearance because of its circumscription, cellular regularity, and lack of mitotic figures. Two of the three reported cases of Jakobiec *et al.* have been followed up for 15 years after enucleation and nine years after iridocyclectomy, with no residual or metastatic disease.[1,2] Follow-up was not reported in the third case.

This case also highlights the dilemma for the clinician when faced with a patient with good vision and a presumptive diagnosis of a malignant melanoma. Should the patient be treated with conservative or radical surgery? We would suggest caution when faced with a tumour in any way atypical on clinical examination and which is also amenable to local excision. In this case the rather whitish appearance of the tumour and the lack of any sentinel vessels and angle involvement influenced the decision to perform local excision.

In summary, we report a case of an extremely rare tumour of the ciliary body, having features of both neurectodermal tissue and smooth muscle. We believe this tumour is correctly termed a mesectodermal leiomyoma.

Dr Valerie White is the recipient of a fellowship award from the Medical Research Council of Canada.

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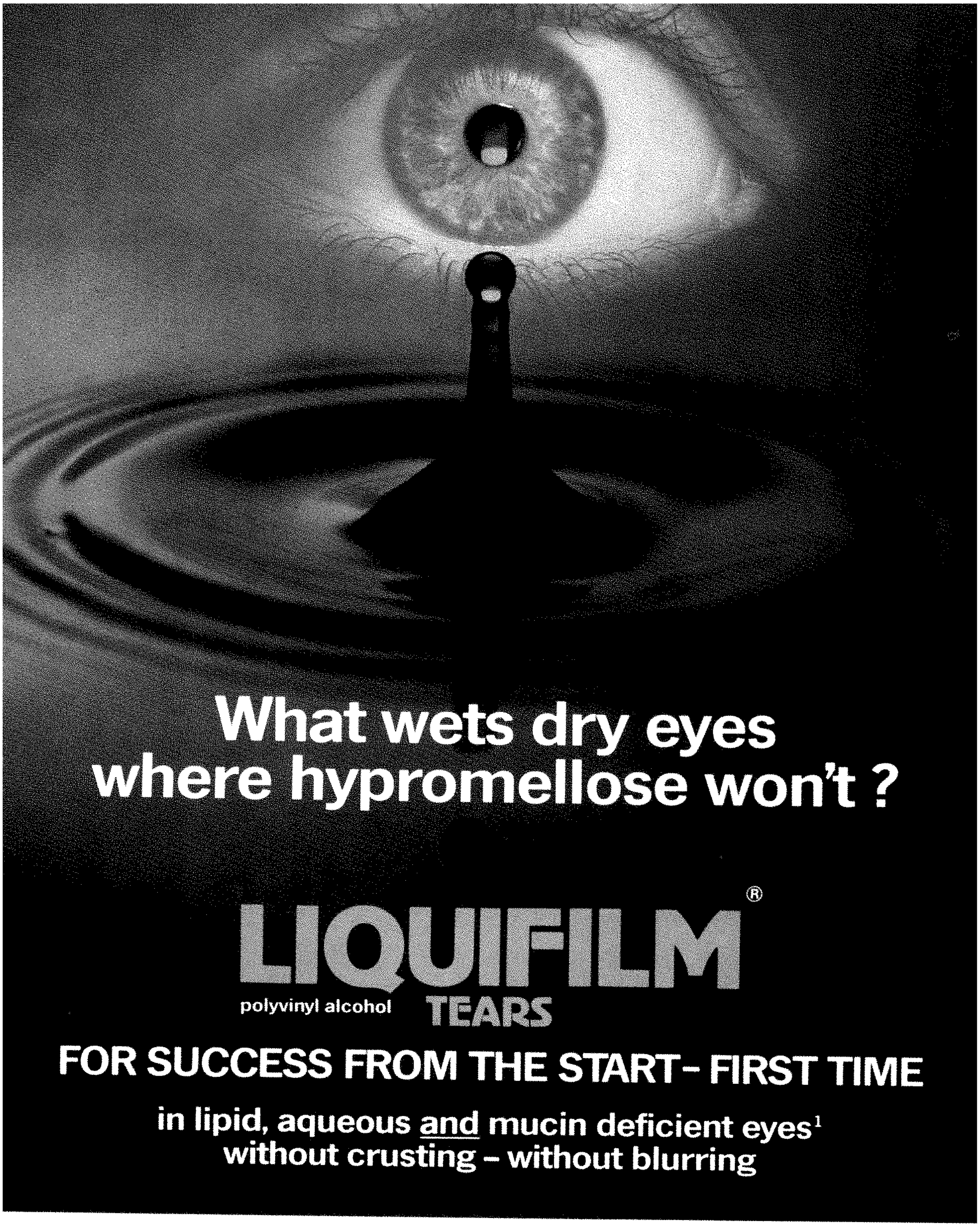
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Reference 1. Kralian LM, American Journal of Optometry and Physiological Optics 1986; **63** (No. 4): 304-308.

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British Journal of Ophthalmology, 1989, **73**, 19–21

Penetrating keratoplasty for corneal scarring due to herpes zoster ophthalmicus

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SUMMARY We retrospectively studied the postoperative results in nine patients with corneal scarring due to herpes zoster ophthalmicus who underwent penetrating keratoplasty. This was a highly selected group that satisfied all of the following criteria: (*a*) absence of active disease of the ocular surface and eyelids, (*b*) intraocular pressure under control, and (*c*) absence of active keratouveitis. Penetrating keratoplasty after herpes zoster ophthalmicus may do well in patients with long preoperative quiescent periods in whom these restrictive preoperative criteria are observed.

Numerous studies have documented extensive involvement of the eye by herpes zoster ophthalmicus (HZO). Nearly every part of the eye can be affected,[1 2] ranging from the eyelids to the retrobulbar structures, including the optic nerve. Corneal disease, occurring in more than half the cases of HZO, is often the primary cause of loss of vision.[3] Corneal involvement includes punctate epithelial keratitis, nummular anterior stromal infiltrates, sclerokeratitis, dendritiform lesions, keratouveitis, endotheliitis, serpiginous ulceration, exposure keratopathy, neurotrophic keratitis, mucous plaques, and immune disciform disease.[2 3] Irreversible corneal scarring, neovascularisation, lipid deposition, thinning, and perforation often result.

In general most patients with herpes zoster keratopathy have been considered poor candidates for penetrating keratoplasty (PKP) because of cornea hyperaesthesia, tear abnormalities, eyelid disease, glaucoma, uveitis, and corneal vascularisation. For these reasons PKP is rarely performed after HZO. We retrospectively examined the surgical results and the associated criteria for selection of patients in nine cases of PKP after HZO.

Patients and methods

The nine cases we reviewed represent all the PKPs performed for corneal scarring due to HZO at the University of Michigan in the past seven years except for one case that was lost to follow-up three months postoperatively. The patients ranged in age from 55 to 86 years (mean age 70) at the time of PKP. Six patients were female and three were male. Postoperative follow-up time ranged from 5 to 40 (mean 18) months. The diagnosis of herpes zoster keratopathy was based on the presence of antecedent skin vesicles and scarring in the ophthalmic division of the trigeminal nerve dermatome. All affected eyes had corneal stromal scarring with central involvement. Each PKP was performed on a previously ungrafted eye.

Preoperatively one patient (case 9) had mild Fuchs's corneal dystrophy and macular oedema in the affected eye. In this patient the main cause of poor vision was the severe corneal scarring due to HZO and not the mild Fuchs's dystrophy. Two patients (cases 6 and 7) had preoperative glaucoma secondary to HZO that was well controlled on topical antiglaucoma agents. Corneal sensations and Schirmer's test with topical anaesthetic were checked preoperatively in all patients. No eyes were noted preoperatively to have active ocular surface or eyelid disorders, such as dry eyes, exposure, rosacea, blepharitis, keratinisation, and trichiasis. No patient had uncontrolled glaucoma or active uveitis at the time of surgery. Thus these nine surgical candidates constituted a highly selected group representing roughly less than 5% of all patients with previous HZO.

Donor corneal tissue was stored in McCarey-Kaufman medium at 4°C within 15 hours after donor

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death and enucleation, and transplanted within 72 hours. During surgery the donor graft was prepared by punching from the endothelial side of the cornea on to a Teflon block with a trephine (8·0 to 9·0 mm). After marking the host cornea with a trephine 0·5 mm smaller, the anterior chamber was entered with either the same trephine or with a razor-blade knife, and the incision was completed with corneal scissors. The donor corneal button was sutured to the host cornea with double-continuous 10-0 and 11-0 nylon sutures and the epithelium was left intact. Three cases (patients 1, 2, and 6) had PKP alone, while in four others (patients 3, 4, 5, and 7) this was combined with extracapsular cataract extraction and posterior chamber intraocular lens implantation. The remaining two cases (patients 8 and 9) had PKP combined with anterior vitrectomy. At the completion of surgery the patients received subconjunctival injections of gentamicin and methylprednisolone. No topical eye medications were given until the first postoperative morning.

Topical prednisolone acetate 1% was then started at least three times a day, but for cases treated by PKP combined with cataract extraction topical corticosteroids were given as often as every two hours around the clock. Two patients received timolol 0·5%, three received mydriatics, one received chloramphenicol 0·5%, and two received artificial tears.

At each daily postoperative slit-lamp examination the epithelium on the graft was assessed with topical fluorescein and checked for defects. Postoperative rises in intraocular pressure were treated with timolol, dipivefrin, and/or acetazolamide. The patients were examined daily for up to five postoperative days until discharge from the hospital, then at one week, three weeks, and at progressively longer intervals. The diagnosis of corneal graft rejection was based on the presence in the donor cornea of keratic precipitates, endothelial rejection lines, or subepithelial infiltrates. The presence of iritis and increased graft thickness constituted an additional, but not necessary, criterion for immune rejection. Graft failure was defined as an irreversibly thick and oedematous, or a scarred and opaque, donor cornea.

Results

Seven of the nine patients had a clear graft at the end of the follow-up period ranging from 5 to 40 (mean 18) months. Six of the patients with clear grafts had a final visual acuity of 20/50 or better. However, one patient with a clear graft (case 7) had a final visual acuity of counting fingers at 2 feet (60 cm) due to macular degeneration with subretinal neovascularisation. Table 1 summarises the clinical findings.

To study the significance of the preoperative quiescent period on the prognosis of the grafts we

Table 1 *Clinical profile of patients*

Patient's number, age, sex	*Corneal sensation*	*Corneal vessels, central/peripheral*	*Time since last activity (months)*	*Postop. F/U (months)*	*Preop VA*	*Best VA/ final VA (postop.)*	*Graft clarity/ cause for ↓ VA*	*Other Dx/procedures in PKP eye*
1/F/55	Normal	−/+ (superficial 1 quadrant)	61	27	20/200	20/20 / 20/20	Clear/NA	None
2/F/69	Marked ↓	−/−	9	5	CF 30 cm	20/40 / 20/50	Clear/NA	Cataract/none
3/M/65	Marked ↓	?/+ (superficial and 360° stromal)	12	12	20/60	20/20 / 20/20	Clear/NA	Cataract/ECCE, PC IOL
4/F/86	Mild ↓	+/+ (stromal 1 quadrant)	24	40	CF 30 cm	20/30 / 20/40−	Clear/NA	Cataract/ECCE, PC IOL
5/F/64	Normal	−/−	44	12	20/70	20/20 / 20/20	Clear/NA	Cataract/ECCE, PC IOL
6/M/56	Absent	+/+ (stromal 360°)	45	17	20/300	20/20 / 20/25	Clear/NA	2° Glaucoma/none
7/M/78	Absent	+/+ (stromal 2 quadrants)	23	7	CF 120 cm	20/200 / CF 60 cm	Clear/macular SRNV	Cataract (glaucoma) macular SRNV/ECCE, PC IOL
8/F/73	Normal	−/−	4	23	CF 180 cm	20/30 / HM	Stromal and microcystic oedema/ graft rejection leading to graft failure	Synechial angle closure, glaucoma/anterior vitrectomy, CCT, conjunctival flap
9/F/80	Marked ↓	−/+ (superficial 1 quadrant)	11	5	CF 30 cm	20/30 / CF 90 cm	Failed/graft failure due to rejection	Cataract, RPE atrophy small disc/anterior vitrectomy PAS lysis, AC IOL

F/U=follow-up, VA=visual acuity, Dx=diagnoses, ↓=decrease, NA=not applicable; ECCE= extracapsular cataract extraction; PC= posterior chamber, AC=anterior chamber; IOL=intraocular lens, CF=counting fingers; HM=hand motions, 2°=secondary, SRNV=subretinal neovascularisation; PBK=pseudophakic bullous keratopathy; CCT=cyclocryotherapy; RPE=retinal pigment epithelium; PAS=peripheral anterior synechiae.

determined the time interval from the acute disease (active HZO) to the time of PKP in each case. This interval ranged from 4 to 112 (mean 39) months. The only two cases that ended in graft failure (patients 8 and 9) had shorter quiescent periods of 4 and 11 months. In both cases graft failure was preceded by immune rejection. Patient 2 underwent PKP after only nine months of quiescence and died after five months of postoperative follow-up; however, the graft remained clear at the time of her death. All other patients with clear grafts had a longer preoperative quiescent period of 23 to 112 months.

The status of preoperative corneal sensation did not correlate with postoperative graft clarity, rejection, or failure (Table 1). Among the seven patients with clear grafts corneal sensation varied preoperatively from briskly intact (cases 1 and 5), mildly decreased (case 4), markedly decreased (cases 2 and 3), to absent (cases 6 and 7). Among the two patients with grafts that underwent immune rejection and eventually failed one (case 8) had intact sensation preoperatively and one (case 9) had markedly decreased sensation.

Preoperative corneal vascularisation was present in six of nine patients and was not correlated with postoperative immune graft rejection. Of these six cases three had superficial corneal vessels (cases 1, 2, and 9) and three had stromal vessels (cases 4, 6, and 7). Of the two patients who had graft rejection one (case 9) had some superficial peripheral vessels preoperatively, while the other (case 8) had no vascularisation.

In all nine cases the epithelium healed completely over the donor cornea within a few days after PKP. No epithelial defects lasted longer than one week, and no patients experienced recurrent epithelial breakdown following the immediate postoperative period.

Discussion

Keratopathy secondary to HZO is a rare indication for PKP in many large reported series. In a study from the Wilmer Ophthalmological Institute which consisted of 1057 consecutive PKPs from 1941 through 1973 only three were for zoster keratopathy.[4] Similarly, of the 710 consecutive PKPs done between 1947 and 1978 at the Estelle Doheny Eye Foundation only three were for zoster keratopathy.[5] Our own experience at the WK Kellogg Eye Center shows that only 10 out of 1359 consecutive PKPs from 1980 through 1985 were for keratopathy due to HZO. The paucity of PKPs done for this indication reflects the widespread understanding that most HZO patients are poor candidates for PKP owing to a neurotrophic cornea, recurrent or chronic inflammation, corneal vascularisation, glaucoma, hypotony, decreased blink frequency, poor viability of corneal epithelium, and disease of the ocular surface, including tear and eyelid abnormalities.[3,6–8] Marsh[7] indicated further that vascularisation of the cornea may be correlated with an increased incidence of post-PKP immune rejection. Many previous reports have specifically cautioned against PKP for HZO for these reasons.[6,9,10] In cases on which we are forced to operate while the eye is actively inflamed (for example, corneal perforation) or in cases of corneal scarring limited to the anterior stroma we prefer lamellar keratoplasty over PKP as a safer procedure.

Our series shows that long-term graft clarity and visual prognosis for zoster keratopathy is improved by the following: (1) longer quiescent waiting period between active disease and surgery, and (2) selection of eyes with minimal preoperative disorders of the ocular surface or neuroretinal or intraocular disease. The later criteria in general skew the selection towards eyes with milder damage due to HZO. Preoperative corneal anaesthesia and vascularisation are of concern and warrant extra attention but did not appear to have any effects in this series.

The present series of nine patients is small owing to the highly selective preoperative criteria. Our experience nevertheless indicates that PKP for zoster keratopathy is not necessarily associated with a dismal prognosis. With fastidious preoperative selection criteria many of the grafted eyes may do quite well in this select group of patients.

The authors thank John Yoon, MD, for his assistance.

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Eikenella corrodens keratitis: case report

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SUMMARY *Eikenella corrodens* is a Gram-negative facultative anaerobe which is part of the normal human oropharyngeal flora and an opportunistic pathogen of mucous membrane tissues. We report a case of secondary *E. corrodens* ulcerative keratitis with hypopyon in a 39-year-old male with herpes simplex keratitis. To the best of our knowledge this is the first reported case of *E. corrodens* as a pathogen in bacterial keratitis.

In 1948 Henriksen described a previously unreported anaerobic Gram-negative bacillus that grew in an unusual pitting pattern on agar.[1] Rather than growing on the surface agar colonies of this organism formed depressions in the media. Because of its growth pattern Holm gave this newly discovered organism the name 'corroding bacillus'.[2] It was not until 1958 that Eiken[3] did a thorough study of the organism, recording the colonial growth patterns and further defining its biochemical properties. From this research he proposed that the bacteria be placed in the genus *Bacteroides* and gave it the name *Bacteroides corrodens*. Further work by Henriksen[4,5] and Jackson *et al.*[6] revealed that a subgroup of *B. corrodens* was in fact not strictly anaerobic. Immunological and nucleotide base pair analysis of this subgroup uncovered properties not consistent with the characteristics of *Bacteroides*. Subsequently this group was removed from the *Bacteroides* genus and renamed *Eikenella corrodens* in the family Brucelleaceae.[7,8]

Eikenella corrodens appears to be part of the normal flora of the human oropharynx. Khairat[9] examined 100 blood cultures one minute after a tooth extraction. He isolated *Eikenella* from 16 of these cultures; in three cases *Eikenella* was the sole isolate. Brooks *et al.*[10] isolated *Eikenella* from 13 out of 40 gingival cultures in clinically uninfected people. These results suggest that *Eikenella* frequently colonises the human upper respiratory tract and that it is capable of invading the blood stream. The first work to document the pathogenic capabilities of this organism was done by Marsden and Hyde,[11] who reported six cases of *Eikenella corrodens* infection in children, including two cases of brain abcess secondary to sinusitis, two gastrointestinal abcesses, a human bite, and a case of sinusitis. In another study at Boston City Hospital retrospective analysis revealed 72 cultures positive for *Eikenella* during 1971–2.[12] Of these isolates 46 were obtained from sputum of bronchial washings, 11 throat or nasopharyngeal cultures, 8 various wounds, 3 abcesses, 2 human bites, a middle ear aspirate, and a tooth socket. This review suggests that *Eikenella*, in addition to frequently being part of the normal flora of the human respiratory tract, can act as an opportunistic pathogen with a predilection for mucous membranes of the respiratory system and gastrointestinal tract.

In the ophthalmic literature Schwartz *et al.* have reported two cases of *Eikenella* infection in orbital cellulitis.[13] In one case the cellulitis was secondary to sinusitis and in the other case there was an infection of an ocular prosthesis after orbital exenteration. Jones and Robinson,[14] in a review of anaerobic ocular infections, reported a case of endophthalmitis following penetrating keratoplasty with positive cultures for *Staphylococcus epidermidis* and *Bacteroides corrodens (sic)*, and also a case of chronic dacryocystitis with a mixed culture that included *Eikenella corrodens*. In an unreported case we have also treated a 72-year-old female with chronic dacryocystitis with cultures positive for two strains of *Eikenella* in mixed flora. To the best of our knowledge this is the first reported case of *Eikenella corrodens* keratitis.

Case report

A 39-year-old male with a history of recurrent herpes simplex keratitis of his left eye since 1967 presented to his ophthalmologist on 20 February 1986 with a

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complaint of discomfort in the left eye. He was diagnosed as having a dendritic lesion on his left cornea and given topical trifluorothymidine every three hours and scopolamine 0·25% three times a day; no antibiotics were given. The patient returned to the doctor three days later complaining of a marked increase in pain and decreased visual acuity. He was noted to have developed a corneal ulcer with hypopyon and was referred to the Palo Alto Veterans Administration Hospital for treatment.

On our initial examination the patient had a visual acuity of 20/20 OD, with adnexa and anterior and posterior segments of the right eye completely within normal limits. His left eye had an acuity of counting fingers at 30 cm. Slit-lamp examination revealed 1+ conjunctival injection and chemosis; the cornea had a 2·5×2·75 mm paracentral epithelial defect, with dense underlying stromal white infiltrate extending to mid stroma, overlying the site of the original dendritic lesion. The anterior chamber had a 1 mm hypopyon. There was no vitreous reaction, and funduscopic examination showed a normal appearance. The patient was admitted to hospital. Prior to antibiotic therapy corneal scrapings were obtained and plated on chocolate, blood, and Sabouraud's agar and thiogylcollate broth media. Empirical therapy of topical cephazolin 100 mg/ml and tobramycin every half hour, and parenteral cephazolin 1 g every eight hours was initiated. On the patient's fourth day in hospital the cultures grew on blood agar a single organism identified as *Eikenella corrodens*. It was sensitive to amikacin, ampicillin, cephamandole, cefoxitin, cephalothin, chloramphenicol, gentamicin, nitrofurantoin, tetracycline, tobramycin, trimethoprim-sulphamethoxazole, and ticarcillin. On this regimen the epithelial defect healed by hospital day eight. On day 10 in hospital the topical cefazolin and parenteral cephazolin were discontinued, and the patient was discharged from the hospital on topical tobramycin. By day 16 of treatment the infiltrate had resolved, and 56 days after the patient's initial presentation he had only a faint central stromal scar. Visual acuity had returned to 20/20. He did not receive steroids at any time during treatment.

Discussion

In recent years the role of anaerobic organisms in ocular infection has come under increased investigation. Jones and Robinson[14] in a review of anaerobic ocular infections report five cases of keratitis. The anaerobic isolates were, in the first case, *Proprionibacterium avidum*, in the second case *Actinomyces viscosus*, and in the third case both *Proprionibacterium acnes* and *Peptococus variabilis*. Cases 4 and 5 both grew *Proprionibacterium acnes*. Four of the five patients had pre-existing epithelial ulceration and stromal inflammation predisposing to opportunistic infection. The antecedent ocular disease in the first case was pseudomonas keratitis, the second case had both herpes zoster and herpes simplex keratitis, the third case had herpes simplex stromal keratitis, the fourth case had had a penetrating keratoplasty, and the fifth had cicatricial pemphigoid. It is of note that two of Jones and Robinson's patients had pre-existing herpes simplex keratitis,[14] as did our patient.

Eikenella corrodens is a Gram-negative bacillus and facultative anaerobe that grows reliably only on blood agar. The optimal growth of the organism is dependent on a haemin concentration of 50 to 250 µg/l of media. Primary isolation is enhanced by a 5–10% carbon dioxide atmosphere *Eikenella* does not grow well in liquid media unless they are enriched with sheep serum or cholesterol.[8]

During the past two decades the role of *E. corrodens* as an opportunistic pathogen in infections of the upper respiratory and gastrointestinal mucous membranes has been well documented.[15] There is no evidence that *Eikenella* is a part of the normal conjunctival flora. Perkins *et al.*[16] cultured, both aerobically and anaerobically the conjunctivae of 273 eyes with conjunctivitis and of 96 normal persons and did not record any *Eikenella* isolates. However, this organism typically is slow growing and frequently requires 24 to 48 hours of incubation before the characteristic pitting colony pattern can be identified. This long period of incubation could cause *Eikenella* in a mixed flora to be overlooked.

This case reinforces the need to consider facultative anaerobic pathogens in keratitis cases, particulary in patients with compromised corneas that may be predisposed to opportunistic infection.

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Bacillus cereus panophthalmitis associated with intraocular gas bubble

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SUMMARY It has become increasingly apparent that *Bacillus cereus* can cause a severe and devastating form of endophthalmitis following penetrating trauma by a metallic object. *B. cereus* is an uncommon aetiological agent in non-clostridial gas-forming infections. The patient studied in this single case report showed evidence of intraocular gas mimicking gas gangrene infection. The physiology of non-clostridial bacteria producing gas from anaerobic metabolic conditions is reviewed. Further intraocular and systemic complications which may be avoided by accurate and early diagnosis and the use of recommended treatment with antibiotics such as clindamycin.

First reported in 1952,[1] *Bacillus cereus* panophthalmitis following penetrating trauma is a serious and very rare type of ocular infection, resulting in enucleation in most cases.[2 3] Owing to the difficulties in identification and taxonomic classification of the *Bacillus* species the specifically appropriate treatment is often delayed. The condition may be further confused by its close similarity to clostridial infection clinically and by the initial Gram's stain interpretation of smears. Since the presence of gas results from anaerobic metabolic conditions, these infections may present as myonecrosis or cellulitis mimicking true gas gangrene. In contrast to gas gangrene there is confusion about the nature, proper classification, and virulent potential of other gas-forming infections.[4] Accurate species identification of the bacillus is important, since the antibiotic of choice for clostridial infections is penicillin while *B. cereus* is resistant to this drug. In view of the extremely destructive and rapidly necrotising nature of *B. cereus* infections[5 6] prompt diagnosis and effective treatment are mandatory.

We report here a case of trauma-induced *Bacillus cereus* panophthalmitis with clinical and CT scan evidence of intraocular gas production. Recognition and early suspicion may help in microbiological diagnosis and facilitate prompt treatment of one of the most destructive infections to afflict the ocular tissues.

Case report

A 28-year-old man presented with a history of penetrating injury of the left eye by a metallic foreign object released while he was hammering on a piece of metal two days earlier. He complained of severe pain, redness, and loss of vision in the affected eye. Examination revealed marked lid oedema, proptosis, complete ophthalmoplegia, and mucopurulent discharge (Fig. 1). The conjunctiva was chemotic and

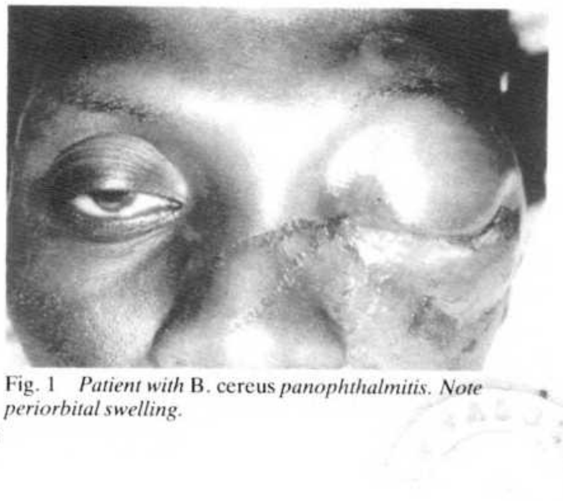

Fig. 1 *Patient with* B. cereus *panophthalmitis. Note periorbital swelling.*

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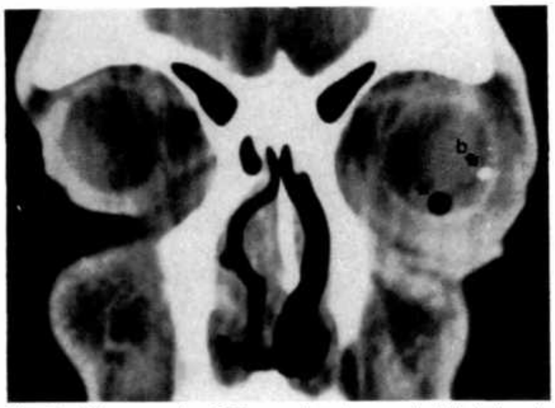

Fig. 2 *Photograph of CT scan showing gas bubble* (a) *and metallic foreign body* (b). *Patient lying on back with neck extended and head lowered.*

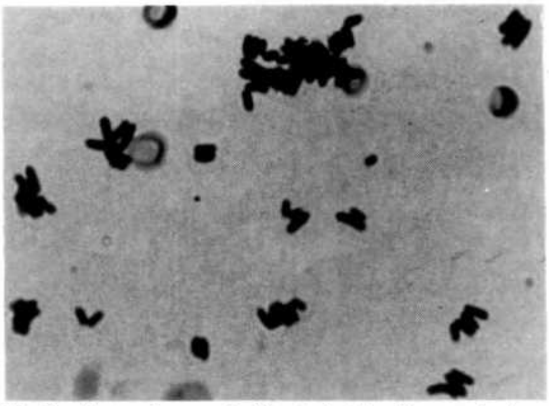

Fig. 3 *Photomicrograph of bacteria taken from cooked meat broth culture. Note pleomorphism. Gram stain,* ×*620.*

prolapsed inferiorly. Biomicroscopy showed severe stromal oedema and total loss of epithelium of the cornea. An entry site was seen in the cornea at 2 o'clock, 3 mm from the limbus. The anterior chamber showed a fibrinoid reaction and hypopyon, with dispersed blood at the pupillary margin. The pupil was fixed and dilated. Lens, vitreous, and fundus could not be seen. The eye was hard to palpation, with increased intraocular pressure.

A CT scan of the left orbit was performed by lying the patient on his back with the head lowered for full neck extension. It showed a dense metallic foreign body and a gas bubble in the globe, with soft tissue swelling of the orbit (Fig. 2). The air bubble moved during the examination.

Cultures were taken from the conjunctiva, cornea, anterior chamber, and vitreous. All specimens were transported to the ocular microbiology service for anaerobic and aerobic culture. The patient was initially started on intravenous gentamicin 80 mg every eight hours and cephazolin 500 mg every six hours, as well as topical fortified gentamicin 14 mg/ml every hour and cephazolin 50 mg/ml every hour. Intravitreal injections of cephazolin (2·25 mg) and gentamicin (0·4 mg) were administered. The patient also received intravenous mannitol (20%) followed by acetazolamide 1 g/day in four divided doses, timolol maleate 0·5%, and propine 0·1% twice daily. The patient was admitted to hospital and this treatment was continued while we awaited laboratory results.

Laboratory findings of the vitreous and anterior chamber fluid revealed numerous polymorphonuclear cells with a mixture of Gram-positive and Gram-negative to variable bacilli seen on direct smears. Gram staining of broth cultures from the anterior chamber revealed many large Gram-positive non-spore-forming rods (Fig. 3). Results from subcultures showed pure growth of β-haemolytic *Bacillus* sp. 48 hours after receipt of specimens. The colony was 4–5 mm, dry, β-haemolytic catalase positive, and glucose, sucrose, maltose, and indole positive. No further isolates were encountered after 14 days' incubation. Results of sensitivity testing showed resistance to penicillin but sensitivity to chloramphenicol and cephalosporin. A specimen was sent to the Center for Disease Control (CDC) in Atlanta, Georgia, for verification, and the organism was identified as *Bacillus cereus*.

The patient deteriorated after three days of treatment. He became febrile (38°C) and had a leucocytosis, the white blood cells being $15{\cdot}9\times10^{9}$/ml with 83% polymorphonuclear cells.

Evisceration of the globe was carried out. Histopathological studies of the ocular contents revealed extensive tissue necrosis and evidence of haemorrhage. Microscopic findings confirmed the diagnosis of acute suppurative endophthalmitis and acute keratitis. The patient was placed on intravenous chloramphenicol 1 g every six hours and topical chloramphenicol 0·5% every four hours for seven days postoperatively.

Discussion

VanBeek and associates[4] reviewed 73 cases of probable non-clostridial crepitant infections with an additional seven recorded by those authors. They proposed a new clinical classification based on the physiology of microbial growth. In-vivo gas production is the end result of anaerobic metabolism by bacteria which are either strict or facultative anaerobes. Any organisms capable of utilising an anaerobic pathway may produce gas if the conditions in the tissue are appropriate. Trauma and surgical and vascular injuries generate areas of tissue anoxia resulting in carbohydrate and protein metabolism proceeding anaerobically, with accumulation of lactic acid.[7] The buffer system in this environment is depleted, and a subsequent decrease in pH occurs, leading to lysosomal disruption and release of autolytic lysosomal enzymes. These in turn release peptides, amino acids, and other reducing substances that may act as microbial substrates. The resulting increase in concentrations of reducing substances coupled with a low pH and anoxia provides an ideal environment for anaerobic microbial metabolism. Gases of varying solubility may be produced by at least three recognised anaerobic pathways: dentrification, fermentation, and deamination.[8]

The genus *Bacillus*, belonging to the family Bacillaceae, is a group of endospore-forming rods of which some are pathogenic for man. They are easily differentiated from other genera of the family by their ability to produce catalase and rod-shaped cells which are aerobic or facultatively anaerobic.[9] *Bacillus* species are capable of utilising an anaerobic pathway to produce both H_2 and CO_2, with variations seen in some strains.[10]

The patient reported on here showed both clinical and radiological evidence of intraocular gas production. Radiologically a definite intraocular gas bubble could be identified, with increased intraocular pressure. There have been two reports of a gas gangrene infection, presumed to be clostridial myonecrosis, which were proved by culture to be *Bacillus cereus* in wound and muscle tissue.[11 12] In both cases the patient was initially treated for a probable *Clostridium perfringens* infection owing to the clinical appearance and the finding of Gram-positive rods in smears. Jonsson and associates[13] reported the first case of simultaneous infection with *B. cereus* and *Clostridium bifermentans* isolated from pleural fluid. In view of the reported resistance to penicillin and grave prognosis of *B. cereus* infections[14] ophthalmologists finding an intraocular gas bubble should be alert to the possibility of *B. cereus* in cases with severe endophthalmitis.

Many saprophytic species of *Bacilllus* have low virulence and are difficult to distinguish from *B. anthracis* except on the basis of pathogenicity. But few laboratories have the facilities to differentiate the many species of *Bacilllus*. There are said to be 400 or more reported species for which little taxonomic information is available.[16] Twenty-two are widely accepted as distinct entities, and 26 others have so far received less widespread recognition. Isolation of *B. cereus*, *B. subtilis*, and *B. laterosporus*[15] from ocular tissue have been previously reported. *B. cereus* has been implicated in food poisoning outbreaks, endocarditis, meningitis, and rarely septicaemia. The DNA base composition indicates that *B. cereus* is most closely related to *B. anthracis*. But unlike *B. anthracis*, *B. cereus* is resistant to penicillin and the cephalosporins owing to the production of extracellular penicillinase and cephalosporinase.[16]

Although it is known that *B. cereus* is not a usual inhabitant of the conjunctival sac, it may become part of the flora,[6] especially in people handling hay or taking care of stables and horses. Tabbara and Burd[17] have isolated *Bacillus* spp. from kohl, which is commonly used by women of Asia, the Middle East, and North Africa as a cosmetic. The widespread use of kohl may increase the incidence of *Bacillus* spp. in the conjunctival cul de sac and thus may increase the risk of bacillus endophthalmitis following trauma.

It has recently become known that this species can result in a virulent endophthamitis with total destruction of the ocular contents, especially if the diagnosis has been delayed. For reasons not known the cornea has a natural resistance to the growth of this organism; only two cases of infectious keratitis due to a *Bacillus* sp. have been reported.[6] Since the vitreous body has no lymphatic system, it may be immunologically compromised and so offer a good medium for the growth of *B. cereus*.

Bacillus cereus ocular infections may be endogenous—usually in intravenous drug abusers[18]—or exogenous—for example, following penetrating trauma by metallic intraocular foreign bodies. A high index of suspicion should be exercised in patients presenting with history of penetrating injury contaminated by soil. Other clues to diagnosis will include a rapidly progressive panophthalmitis with fever and leucocytosis, much like that of *Clostridium perfringens*, which differs from other micro-organisms causing endophthalmitis in not producing systemic signs.

Once diagnosis is suspected, a vitreous tap should not be delayed. Clindamycin, if given in the therapeutic range in the vitreous, has been found to be effective in the treatment of these infections.[19] Liesegang[20] has suggested that a method of inactivating the exotoxins responsible for the severe necrosis in panophthalmitis should be investigated. Early recognition and institution of therapy directed specifically against *B. cereus* must be initiated early, for the speed with which irreversible changes occur leaves a very short time to save the eye.

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Levels of zinc in plasma, erythrocytes, and hair, and levels of serum copper in patients with retinitis pigmentosa in Turkey

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SUMMARY This study was made on 100 patients with retinitis pigmentosa and 23 of their relatives. Their plasma, erythocyte, and hair Zn and serum Cu levels were compared with those of a control group of 14 healthy persons. No statistically significant difference in these levels was found between the patients with retinitis pigmentosa and the relatives or controls.

For the past 20 years zinc has been a trace element of interest to nutritionists, medical researchers, and clinicians. Zinc has been found to be involved in many eye functions, for example, rod functions and dark adaptation. Normal rod functions and dark adaptation require that rhodopsin be produced from retinol. This in turn requires retinal reductase enzymes which have zinc as the activating constituent.

There are few studies on trace elements in retinitis pigmentosa.[1-11] In 1976 Gahlot *et al.*[2] reported on the relation between copper and zinc metabolism in retinitis pigmentosa. They measured serum copper and ceruloplasmin and 24 hour urine copper levels in retinitis pigmentosa. There are few studies on zinc metabolism in retinitis pigmentosa. In the present study, in addition to the plasma zinc and serum copper levels, we measured the erythrocyte and hair zinc levels.

Material and methods

The study was made on 100 patients with retinitis pigmentosa and their 23 healthy relatives The results were compared with those from a control group of 14 healthy persons of similar socioeconomic class.

The group of 100 patients with retinitis pigmentosa comprised 73 men and 27 women, the 23 relatives 18 men and 5 women, and the control group 5 men and 9 women. The age of the patients with retinitis pigmentosa ranged from 11 to 71. The average age was 31 in the retinitis pigmentosa group, 23 in the relatives, and 18 in the controls. A complete history was obtained from all patients with retinitis pigmentosa, and medical and ophthalmological examinations were performed. In the ophthalmological examinations, in addition to routine visual tests, both eyes of all the patients were examined by Goldmann's three-mirror contact lens, Goldmann's kinetic perimetry, fluorescein angiography, and colour fundus photography.

Those who were pregnant, taking birth control medication, on other medication or suffering from any systemic disease which might effect their Cu/Zn metabolism were eliminated

Blood and hair samples were taken from the 137 study participants by one supervised technician All the samples were taken between 0800 and 0900 following a complete fast of at least 12 hours. The samples were transferred to the Zn Deficiency and Treatment Unit, where they were tested under the control of one of the authors.

The hair samples were investigated by the method suggested by Schroeder and Nason.[12] The 2380 model Perkin Elmer atomic absorption spectrophotometer was used.

The statistical comparisons were made by the Barlett χ^2 test method. Nine additional parameters were analysed statistically.

This study was supported by the Zn Deficiency Treatment Unit established by the Turkish Scientific and Technical Research Council (TUBITAK) in the Paediatric Clinic, Ankara University.

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Results

No statistically significant difference was found between the average plasma, erythrocyte, and hair zinc and serum copper levels of the patients with retinitis pigmentosa and those of the relatives and controls, nor was sex found to be a significant factor (Table 1).

The duration of the retinitis pigmentosa showed no correlation with the plasma, erythrocyte, and hair zinc and serum copper levels (Table 2).

No statistically significant difference was found between the plasma, erythrocyte, and hair zinc and serum copper levels of 21 patients with retinitis pigmentosa and those of the 23 persons who were their relatives (Table 3).

No statistically significant correlation was found between the average plasma, erythrocyte, and hair zinc and serum copper levels and the visual acuity evaluated in the 192 eyes of 96 patients with retinitis pigmentosa (Table 4).

Visual field defects in patients with retinitis pigmentosa were classified as mild, generalised, or tubular. The type and the quantity of the visual field defects had no correlation with the average plasma, erythrocyte, and hair zinc and serum copper levels (Table 5).

In patients with retinitis pigmentosa having additional fundus changes (such as degeneration of the macula and retinal haemorrhages) Zn and Cu levels showed no statistically significant changes compared with the controls (Table 6). Likewise the anterior segment pathology in patients with retinitis pigmentosa did not influence the above mentioned Zn and Cu levels compared with the controls (Table 7).

Although the average hair Zn level in patients with retinitis pigmentosa was higher than that in the controls, the difference was not statistically significant (Table 8).

Table 1 *Zn and Cu levels in retinitis pigmentosa patients, unaffected relatives, and controls, mean (SEM), by sex*

	Plasma Zn μg/100 ml (SEM)	*Red corpuscle μg/ml (SEM)*	*Serum Cu μg/100 ml (SEM)*
RP patients			
Male	80·85 (1·75) (n: 72)	12·24 (0·25) (n: 72)	111·71 (4·43) (n: 57)
Female	78·64 (3·05) (n: 24)	12·16 (0·34) (n: 26)	116·73 (6·93) (n: 26)
Total	80·35 (1·51) (n: 96)	12·21 (0·20) (n: 98)	113·26 (3·72) (n: 83)
Relatives			
Male	79·44 (3·58) (n: 17)	12·07 (0·45) (n: 17)	111·94 (8·63) (n: 13)
Female	77·0 (4·46) (n: 5)	11·41 (1·03) (n: 5)	131·4 (18·23) (n: 5)
Total	78·20 (2·38) (n: 22)	12·20 (0·42) (n: 22)	109·25 (8·19) (n: 18)
Controls			
Male	83·8 (2·24) (n: 5)	13·82 (0·84) (n: 5)	124·5 (24·05) (n: 4)
Female	77·89 (4·02) (n: 9)	12·4 (0·68) (n: 9)	115·41 (11·50) (n: 8)
Total	80·57 (3·86) (n: 14)	12·90 (0·53) (n: 14)	121·65 (10·28) (n: 12)

RP=retinitis pigmentosa. $p>0\cdot05$ not significant
SI conversion: (μg×10)/100 ml=μg/l

Table 2 *Zn and Cu values of RP patients by duration of RP, mean (SEM)*

Duration (years)	*Plasma Zn μg/100 ml (SEM)*	*Red corpuscle Zn μg/ml (SEM)*	*Serum Cu μg/100 ml (SEM)*
≤5	82·05 (2·62) (n: 20)	11·97 (0·49) (n: 20)	112·77 (6·80) (n: 18)
6–10	79·55 (2·54) (n: 39)	12·23 (0·27) (n: 49)	115·70 (5·55) (n: 33)
11–20	79·47 (3·50) (n: 24)	12·63 (0·46) (n: 25)	110·46 (5·81) (n: 20)
>21	81·76 (3·27) (n: 13)	11·80 (0·64) (n: 13)	112·10 (16·16) (n: 12)

RP=retinitis pigmentosa $p>0\cdot05$ not significant
SI conversion: (μg×10)/100 ml=μg/l.

Table 3 *Zn and Cu values of RP patients compared with those of unaffected relatives, mean (SEM)*

	Plasma Zn μg/100 ml (SEM)	*Red corpuscle Zn μg/ml (SEM)*	*Serum Cu μg/100 ml (SEM)*
RP patients	78·64 (3·37) (n: 21)	11·66 (0·41) (n: 22)	126·10 (8·38) (n: 21)
Relatives	78·20 (2·38) (n: 22)	12·20 (0·42) (n: 22)	109·25 (8·19) (n: 18)

RP=retinitis pigmentosa. $p>0\cdot05$ not significant
SI conversion: (μg×10)/100 ml=μg/l.

Table 4 *Zn and Cu values by visual acuity of eyes with RP, mean (SEM)*

Visual acuity	*Plasma Zn μg/100 ml (SEM)*	*Red corpuscle Zn μg/ml (SEM)*	*Serum Cu μg/100 ml (SEM)*
Abs-PP	79·47 (2·01) 60 eyes	12·79 (0·27) 58 eyes	113·58 (5·57) 52 eyes
5 cm CF	76·60 (2·16) 46 eyes	12·30 (0·25) 50 eyes	115·95 (5·55) 43 eyes
0·1–0·5	83·37 (1·97) 60 eyes	11·83 (0·25) 61 eyes	108·61 (4·12) 46 eyes
0·6	75·62 (2·04) 24 eyes	12·09 (0·48) 23 eyes	117·39 (5·19) 23 eyes
Total RP eyes	192	196	166

RP=retinitis pigmentosa. CF=counting fingers. Abs-PP=absolute perception and projection $p>0\cdot05$ not significant.
SI conversion (μg×10)/100 ml=μg/l.

Table 5 *Zn and Cu values by reduction in visual field, mean (SEM)*

Degree of constriction	*Plasma Zn μg/100 ml (SEM)*	*Red corpuscle Zn μg/ml (SEM)*	*Serum Cu μg/100 ml (SEM)*
Mild	75·07 (2·73) (n: 19)	11·44 (0·44) (n: 22)	116·29 (6·34) (n: 17)
Generalised	85·02 (4·12) (n: 19)	11·64 (0·37) (n: 20)	120·78 (9·75) (n: 14)
Tubular	81·73 (3·13) (n: 17)	12·26 (0·53) (n: 13)	110·30 (8·57) (n: 15)

p>0·05 not significant.
SI conversion (μg×10)/100 ml=μg/l.

Table 6 *RP patients with additional fundus changes compared with healthy controls, mean and (SEM)*

	Plasma Zn μg/100 ml (SEM)	*Red corpuscle Zn μg/ml (SEM)*	*Serum Cu μg/100 ml (SEM)*
RP patients	75·79 (3·04) (n: 17)	12·24 (0·38) (n: 17)	115·76 (7·67) (n: 16)
Controls	80·57 (3·86) (n: 14)	12·90 (0·53) (n: 14)	121·69 (10·28) (n: 12)

RP=retinitis pigmentosa. p>0·05 not significant
SI conversion (μg×10)/100 ml=μg/l.

Table 7 *RP patients with anterior segment pathology compared with healthy controls, mean (SEM)*

	Plasma Zn μg/100 ml (SEM)	*Red corpuscle Zn μg/ml (SEM)*	*Serum Cu μg/100 ml (SEM)*
RP patients	75·58 (1·81) (n: 42)	12·63 (0·32) (n: 41)	112·23 (5·87) (n: 39)
Controls	80·57 (3·86) (n: 14)	12·90 (0·53) (n: 14)	121·69 (10·28) (n: 12)

RP=retinitis pigmentosa p>0·05 not significant
SI conversion: (μg×10)/100 ml=μg/l

Table 8 *Hair Zn values in RP patients and healthy controls, mean (SEM)*

	Hair Zn (μg/g (SEM)
PR patients	175·63 (7·9) (n: 81)
Healthy controls	146·34 (10·24) (n: 15)

RP=retinitis pigmentosa p>0·05 not significant

Discussion

The main purpose of this study was to investigate whether any relation existed between retinitis pigmentosa and zinc metabolism. Previously only the relation of copper metabolism to retinitis pigmentosa had been extensively studied; only a few studies had been made on the relation between zinc metabolism and retinitis pigmentosa.[1, 9–11]

This study showed no significant change in the average plasma, erythrocyte, and hair zinc levels in retinitis pigmentosa. In addition, the Zn levels showed no correlation with the duration and seriousness of the retinitis pigmentosa. Although we found an obviously low level of Zn in the plasma, erythrocytes, and hair in some patients with retinitis pigmentosa, this low level could not certainly be attributed to the retinitis pigmentosa, since a low level of Zn might have several causes.

Our findings did not confirm the studies of Gahlot *et al.*, who had reported that disorders of copper metabolism were characteristic for retinitis pigmentosa. In 1977 Ehlers and Bülow found a normal Cu metabolism in patients with retinitis pigmentosa.[3] This result was confirmed by Marmor *et al.* in 1978.[4] In 1982 Mota *et al.* also found no change in the Cu metabolism in patients with retinitis pigmentosa.[5]

In 1981 Sangameswar *et al.* found a partial change in the copper metabolism of the patients with retinitis pigmentosa.[6]

We found in comparison with controls that neither serum Cu levels nor Zn metabolism in retinitis pigmentosa showed any significant changes.

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Retinal and choroidal vascular occlusion secondary to corticosteroid embolisation

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SUMMARY We report a case of visual loss following intranasal injection of triamcinolone acetonide and phenylephrine hydrochloride in a 22-year-old female with chronic sinusitis. Clinical examination and fluorescein angiography revealed vascular occlusions which involved multiple small branches of both the choroidal and retinal circulations. The mechanism of such a complication probably involves inadvertent intra-arterial injection into the anterior or the posterior ethmoidal artery, with retrograde flow into the opthalmic arterial system. Precautions can be taken to avoid such complications.

Ocular complications may follow therapeutic injections around the eyes, nose, lips, and scalp.[1-4] The first reports of blindness following intranasal injections of warm paraffin were decribed in the early 1900s.[1] The beneficial effects of corticosteroids became apparent in the early 1960s, and instances of unilateral or bilateral visual loss immediately following extraorbital corticosteroid injections have been described subsequently.[5] We report a case of transient visual loss with combined choriocapillaris and retinal arteriolar occlusion following an intranasal injection of corticosteroid and phenylephrine hydrochloride.

Case report

A 22-year-old-female with a history of chronic sinusitis was given an injection of triamcinolone acetonide (Kenalog) and phenylephrine hydrochloride in both inferior nasal turbinates. 1 ml containing 20 mg of trimacinolone acetonide was injected first uneventfully in the left turbinate. After waiting two minutes an additional 1 ml with 20 mg of triamcinolone acetonide was injected in the right turbinate. The physician encountered an unusual amount of resistance during the injection, and the injection required much more force than usual to complete. Immediately after the injection the patient noted a marked loss of vision in her right eye. She was seen within several hours by her ophthalmologist. Vision at that time was noted to be counting fingers in the right eye, and a 3+ relative afferent pupillary defect was present. On ophthalmoscopy multiple foci

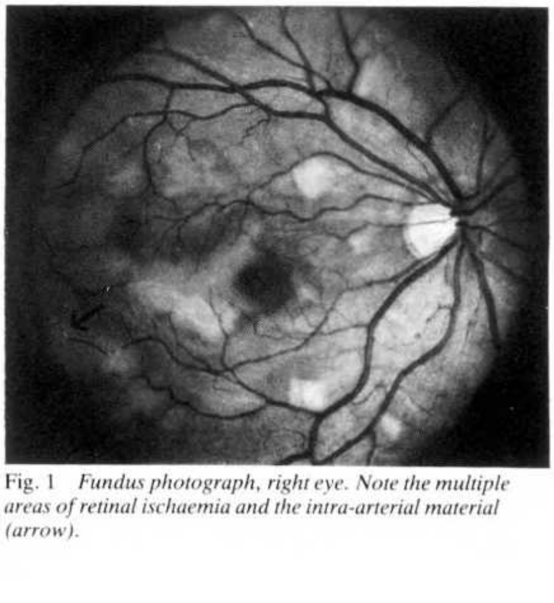

Fig. 1 *Fundus photograph, right eye. Note the multiple areas of retinal ischaemia and the intra-arterial material (arrow).*

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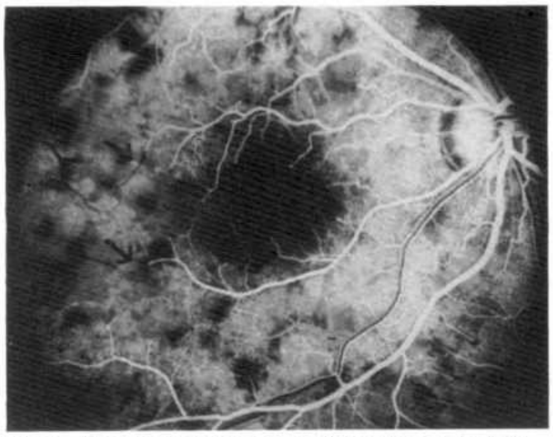

Fig. 2 *Fluorescein angiogram, early arteriovenous phase. Areas of choroidal non-perfusion and retinal arteriolar obstruction (arrows) are present.*

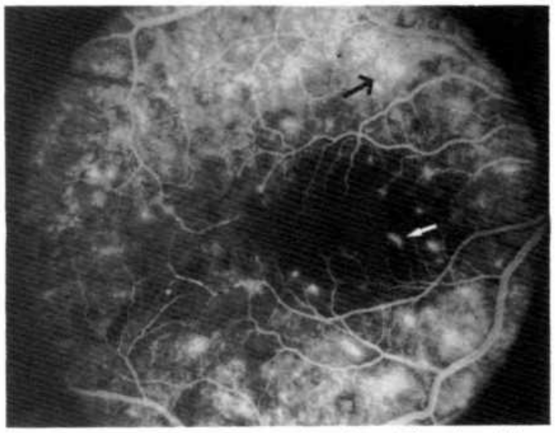

Fig. 3 *Fluorescein angiogram, late phase. There is staining of some of the retinal vessels (lower arrow) and focal areas of choroidal hyperfluorescence (upper arrow).*

of intra-arteriolar, small, plaque-like, whitish material were seen in the temporal macular vessels of the right eye.

Twenty-four hours later she was seen by one of us (KAG). At that time the visual acuity was 20/400 in the right eye and 20/20 in the left. A 2+ relative afferent pupillary defect was present in the right eye. Ophthalmoscopic examination revealed multiple areas of retinal ischaemia in the macula and the same intra-arteriolar material (Fig. 1). The retinal arterioles temporal to the macula appeared to be occluded, but the optic nerve was normal. The left eye was normal. Goldmann visual field examination revealed an inferior altitudinal defect with peripheral constriction of the remaining superior field. Fluorescein angiography (Fig. 2) in the early phases revealed several randomly scattered, small, irregular zones of choroidal hypofluorescence. In addition retinal arteriolar filling defects were present in the temporal paramacular area. Fluorescein leaked from these retinal vessels during the late phases of the fluorescein angiogram, and small hyperfluorescent zones in the choroid were present which slowly increased in size (Fig. 3). These findings were thought to be consistent with multiple microemboli to the chroroidal and retinal circulations, presumably from the local corticosteroid injection. No specific treatment was given.

Four days after the first visit the fluorescein angiogram was repeated and was found to be normal. A subsequent fluorescein angiogram two months later was within normal limits as well, and no retinal pigment epithelial changes were detected. One year later the patient was asymptomatic, had recovered 20/20 vision, and had a normal visual field.

Discussion

It is thought that retinal and choroidal emboli following injections in areas remote from the eye, such as the nose, may occur as a result of inadvertent intra-arterial injection of the drug.[1-4] The ophthalmic artery branches peripherally into the anterior and posterior ethmoidal arteries, which supply the nasal mucosa. These vessels anastomose with branches of the external carotid artery in the face. Inadvertent injection of small particles under pressure into an anterior ethmoidal artery can cause retrograde flow into the ophthalmic artery, which then can enter the eye via the central retinal artery and the short posterior ciliary arteries.[4] Therapeutic agents injected under pressure into a chronically inflamed tissue with a sinusoidal vascular system may gain access to the supplying arteries as well.[6]

The patient described herein demonstrated non-perfusion of some of the retinal arterioles and lobules of the choriocapillaris. Corticosteroid emboli from the injection were the probable cause of these combined retinal and choroidal vascular occlusions, though vasospasm induced by the phenyephrine hydrochloride which was added to the injection solution may have been a contributing factor.

The outcome in this instance was fortunately favourable, with full visual recovery. Other workers, however, have reported unilateral and bilateral visual loss following embolisation of material injected in the head and neck.[3] To avoid potential complications precautions should be taken in administering such injections. The use of a decongestant such as epinephrine or cocaine applied to the turbinates prior to the injection may be useful.[4]

Proprioceptive awareness of syringe resistance may facilitate safe injection. Aspiration prior to injection should always be performed; however, local collapse of the microvasculature may give a falsely negative aspiration, and insufficient resistance on injection may signify an intra-arterial injection.[5] Injecting slowly, in small quantities, and moving the needle while injecting to avoid placing a large bolus of material in one location have been advocated.[4] In addition, when possible, using suspensions that have small particles may be beneficial, as suspensions with larger particles are more likely to cause significant vascular occlusion should embolisation occur.[4,5]

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A new synthetic material for the brow suspension procedure

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SUMMARY This report describes the use of a new synthetic material, combining polyester with carbon, in nine brow suspension procedures. The mechanical properties of polyester, with the fibrous tissue inducing properties of carbon, combine to produce a scaffolding on which fibrovascular ingrowth is possible. Subsequent fibrosis gives a permanent effect. Early results indicate that the material is tolerated well in the eyelid, but the problem of early slippage remains.

The brow suspension procedure also known as frontalis sling or frontalis suspension is the treatment of choice for ptosis characterised by minimal levator function and a narrow interpalpebral aperture.[1-5] Many methods of brow suspension have been advocated, but the use of autogenous fascia lata remains the most popular and the most effective.[6] However, this technique is not possible in children under 3 years old because the fascia lata has not developed sufficiently in them.[7] Stored irradiated fascia and lyophilised fascia have been recommended, but the results are less satisfactory, and fascial banks are necessary for storage.[8] A further alternative is to use extensor tendons which are sufficiently developed by the age of 6 months and make suitable material.[9]

Many synthetic materials have been used, the most popular being a polyester cable type (Supramid). A high incidence of granuloma formation, progressive loosening, and fracture has been recorded with this material.[10] This report describes early experience with a new synthetic material which combines polyester and carbon.

Materials and methods

Each child selected for this procedure had severe ptosis with minimal levator function. The timing of surgery was dictated by the severity of the ptosis and the associated problems of compensatory head posture and occlusion of the visual axis. Fox's technique was employed and adapted for use with this material.[4] A Frost suture was placed in the lower lid on completion of surgery and was removed on the second postoperative day. Topical lubrication was applied on a regular basis for two to six weeks. The child was assessed on the second day and at two, six, and 12 weeks after surgery.

The new suture material used is called the ABC (Active Bioprosthetic Composite) ligament and tendon repair material; it is produced by Surgicraft Ltd (Britten Street, Redditch, Worcs B97 6HF, England).

Early reoperation was required in one child because of immediate surgical failure. At surgery a biopsy of the old suture track was taken, and this was examined by both light and electron microscopy (Figs. 1, 2).

Results

Nine brow suspension procedures were carried out on five children. Follow-up ranged from three to seven months, mean five months, and there have been no instances of wound infection, stitch granuloma, fistula, or tattooing in the follow-up period.

Patient 1 was a 4-year-old girl with mitochondrial cytopathy and bilateral ptosis. The interpalpebral apertures measured 3–4 mm, and surgery resulted in the apertures measuring 7 mm for the right eye and 9 mm for the left eye.

Patient 2 was a 3-year-old girl with bilateral congenital ptosis. The right interpalpebral aperture measured 4 mm, requiring surgery. The immediate

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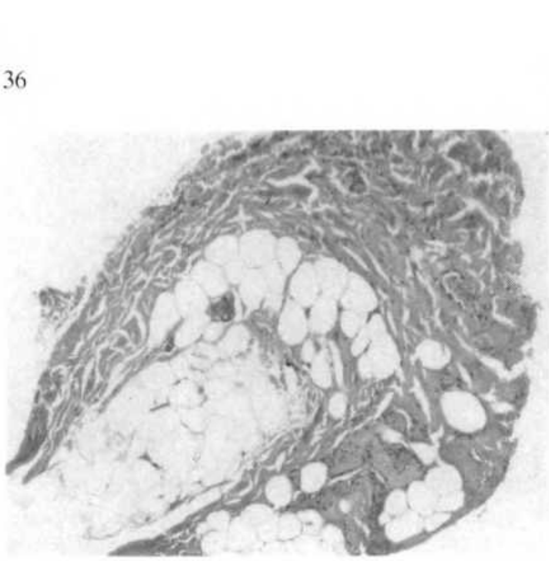

Fig. 1 *Collagen and adipose tissue, with no evidence of granuloma or residual suture material. Haematoxilin and eosin, ×100.*

postoperative result was poor, and a levator resection was subsequently performed seven months later. A biopsy of the original suture track was obtained, and, though a well defined cord-like structure was identified, both light microscopy and electron microscopy studies showed fibrous tissue and adipose tissue only. No suture material was identified (Figs. 1, 2). Patient 3 was a 9-year-old girl with bilateral congenital ptosis, the upper lids just clearing the pupil, with no demonstable levator function. The immediate postoperative results were good in both eyes and maintained in the left, but the right lid returned to its original position by the second week. The skin crease also disappeared, and it is likely that the suture material slipped.

Patient 4 was a 22-month-old boy with bilateral ptosis. The interpalpebral apertures measured 4 mm in the right eye and 5 mm in the left. Surgery resulted

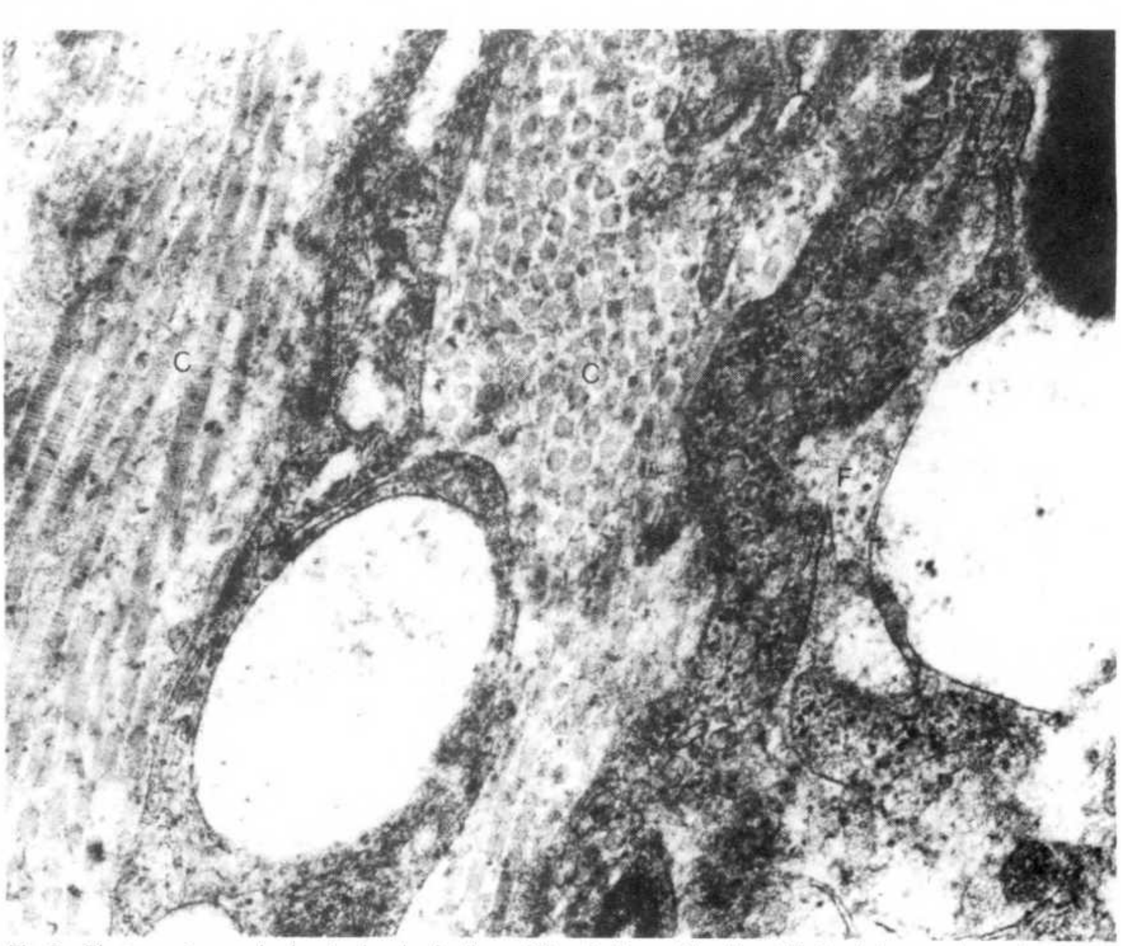

Fig. 2 *Electron micrograph, showing bands of collagen* (C) *and adjacent fibroblasts* (F). *Lead citrate and uranylacetate, ×518 500.*

in apertures measuring 7 mm in the right eye and 8 mm in the left eye.

Patient 5 was a 14-month-old boy with bilateral congenital ptosis. The interpalperbral apertures measured 5 mm, and initially brow suspension procedures using nylon were performed. Both subsequently slipped within two years, and brow suspension procedures were again performed with the new material when he was aged 4 years. The interpalpebral apertures eventually returning to 8 mm in the right eye and 7 mm in the left eye.

Discussion

It is not known when the repair of ptosis was first attempted. There are reports that Celsus in the first century AD described excision of eyelid skin.[11] This was again proposed by Arabian surgeons and subsequently adopted and modified by Scarpa in 1801, Hunt in 1830, and others.[12] The levator muscle was replaced in various ways and the superior rectus muscle incorporated, often with limited success.[12]

The use of the frontalic muscle to elevate the lid by attaching the upper border of the tarsus subcutaneously to the muscle overlying the eyebrow is now the treatment of choice in severe degrees of ptosis with limited levator function. Various materials have been used, including skin,[13] levator tendon,[14] orbicularis muscle,[15] frontalis muscle strips,[12] or corrugator supercalii strips.[12]

Payr was the first to use autogenous fascia lata as a sling.[16] Wright[17] described the technique in detail, and it was later modified by Crawford.[18] Fascia lata remains the most popular material, as it is capable of producing a permanent effect, probably because it retains its cellular viability.[19] The requirement for a second operative site to obtain autogenous fascia lata and the lack of suitable tissue in children under the age of three years have been major drawbacks. Banked allogeneic fascia lata obviates these difficulties but has not been widely used because of its relative inaccessibility and a potentially lower success rate. Lyophilised fascia has been used, and there is histological evidence that this is replaced by the recipient's own fibroblasts, suggesting that this may also be capable of producing a permanent effect.[20] In the short term this has proved to be effective, though there is a significant incidence of slippage within the first three months.[8]

Other materials, including tendon,[9 21] preserved sclera,[22] sutures such as catgut and silk, metals such as gold, silver, and platinum, silicone threads or strips, and stainless steel wire springs have also been tried.[12] The most widely used synthetic material is a polyfilament cable type suture, which has the advantages of ease in handling and commercial availability but does have an increased incidence of granuloma formation, progressive loosening, susceptibility to trauma, and eventual failure.[8]

Factors that need to be considered in the development of a new material include accessibility, infection and rejection rates, ease of handling, degree of permanency, granuloma and fistula formation, and tattoo rates. The degree of permanency may depend on the ability of the material to provoke a fibroblastic reaction, as is seen with fascia lata.

A bioprosthetic ligament material made of an assembly of carbon and polyester fibres is now being used in knee ligament surgery [23] Both materials have been used independently for this is the past and have shown the so-called 'new ligament' effect by acting as a biological scaffold for the ingrowth of mesenchymal cells, which lay down collagen tissue and its supporting vascular elements.[24] This mechanism has therefore enabled the repair and reconstruction of ligaments and tendons in both humans and animals.[25] Its effect has been confirmed histologically in man[26] and seen in several different anatomical sites.[27] Neither of the materials in isolation shows an ideal mechanical behaviour under stress, but, when combined, the polyester fibres are prevented from overextension by the carbon fibres, which are in turn protected from the sheer stresses by the polyester.[28] Polyester is more resilient and handles more readily, carbon fibres are more likely to become infiltrated by and incorporated into fibrous tissue.[29]

This paper reviews our early experience with this material in the subcutaneous tissue of the eyelid as a frontalis sling All patients had a minimal follow-up period of three months.

The new material handled well. It was smooth, firm, resilient, and easy to tie. The functional results of surgery were comparable with any series of brow suspension procedures. The children appeared to tolerate the procedure well, and bruising was minimal. Cosmetically acceptable results were recorded in all nine operations.

None of the procedures were complicated by fistula formation, granuloma, infection, or tattooing. It seems therefore that this material is safe to use in the eyelid.

During the first three months the surgical objective was achieved in all but two lids. Failure was immediate in both instances and almost certainly due to slippage. A biopsy of the suture track taken from one patient seven months after the original surgery revealed fibrous tissue and adipose tissue only. There was no sign of added fibroblastic activity or suture material. It is assumed that the suture material retracted back after early slippage into the brow, resulting in a limited response. Previous biopsies at operation sites have shown a predictable response, with evidence of the suture material (Strover AE, personal communication, 1987).

CONCLUSION

This new material may provoke the fibrous tissue reaction seen when using fascia lata and responsible for the permanence of the result. It appears to be tolerated well in the first three months, but it remains to be seen from long-term follow-up how effective the material really is.

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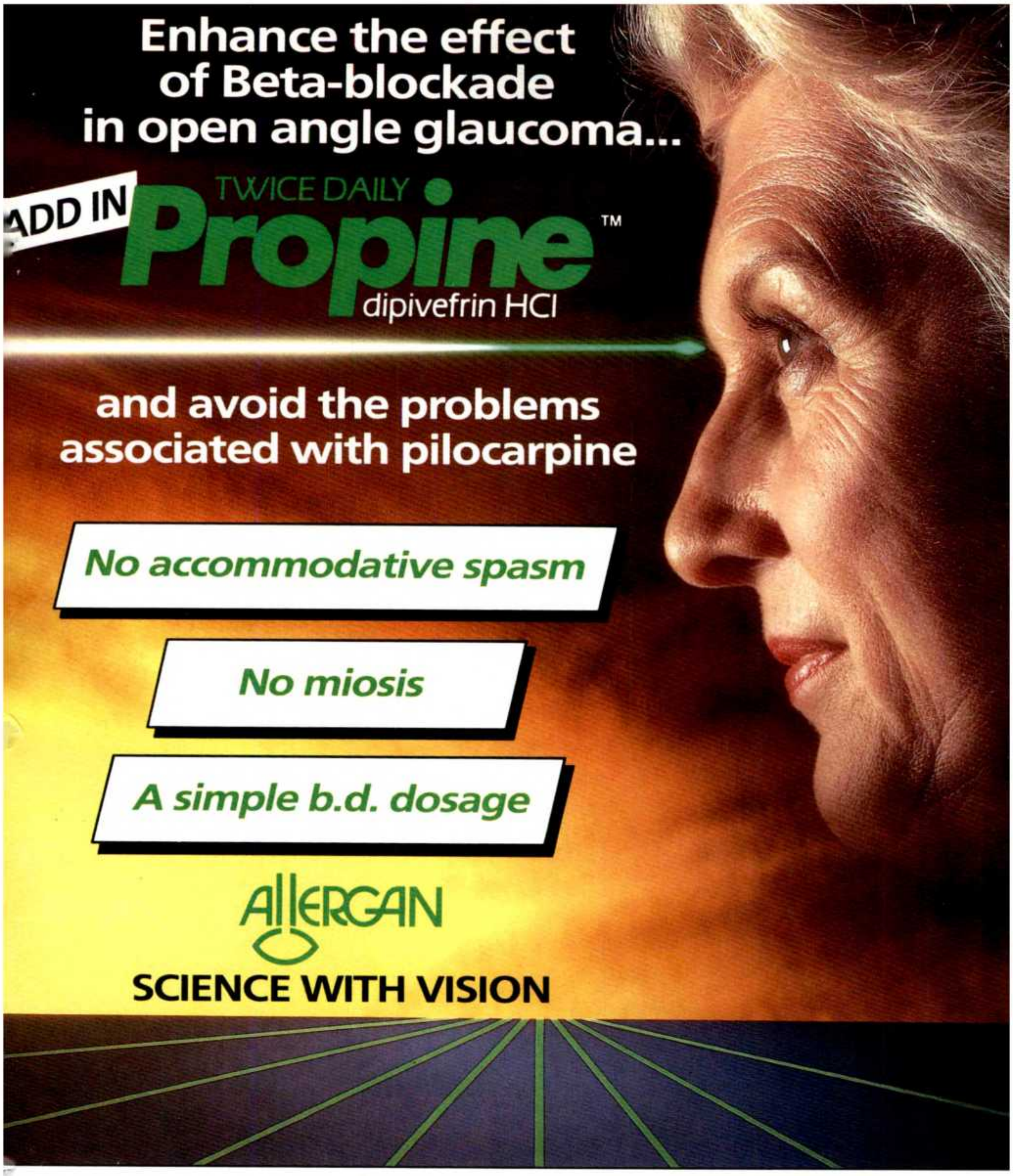

PROPINE™ Prescribing Information

Presentation Sterile ophthalmic solution containing dipivefrin hydrochloride USP 0.1% (w/v). Also contains benzalkonium chloride Ph Eur 0.005% (w/v), disodium edetate Ph Eur 0.015% (w/v), with sodium chloride Ph Eur and purified water Ph Eur. **Uses** For the control of intraocular pressure in chronic open angle glaucoma or ocular hypertensive patients with anterior chamber open angles. **Dosage and administration** The usual dosage is one drop in the affected eye(s) every 12 hours. **Contra-indications, warnings, etc.** *Contra-indications:* patients suffering from closed angle glaucoma. *Use in pregnancy:* the safety of intensive or protracted use of dipivefrin during pregnancy has not been substantiated. *Precautions:* dipivefrin should be used with caution in patients with narrow angles since dilation of the pupil may trigger an attack of angle closure glaucoma. Macular oedema is a rare occurrence with adrenaline use in aphakic patients. Prompt reversal generally follows discontinuance of the drug. Macular oedema with dipivefrin does present as a possibility in the aphakic patient. *Adverse reactions:* rebound vasodilation and allergic blepharoconjunctivitis are rarely observed following treatment with dipivefrin. Dipivefrin has been used successfully in patients who demonstrated such intolerance to adrenaline. Adrenochrome deposits have been rarely observed following use of dipivefrin. Very slight transitory stinging may occur upon instillation in some patients. This product contains benzalkonium chloride and should not be used by patients continuing to wear soft (hydrophilic) contact lenses. **Pharmaceutical precautions** Store at room temperature. Discard any unused contents 28 days after opening the bottle. **Legal category** POM.
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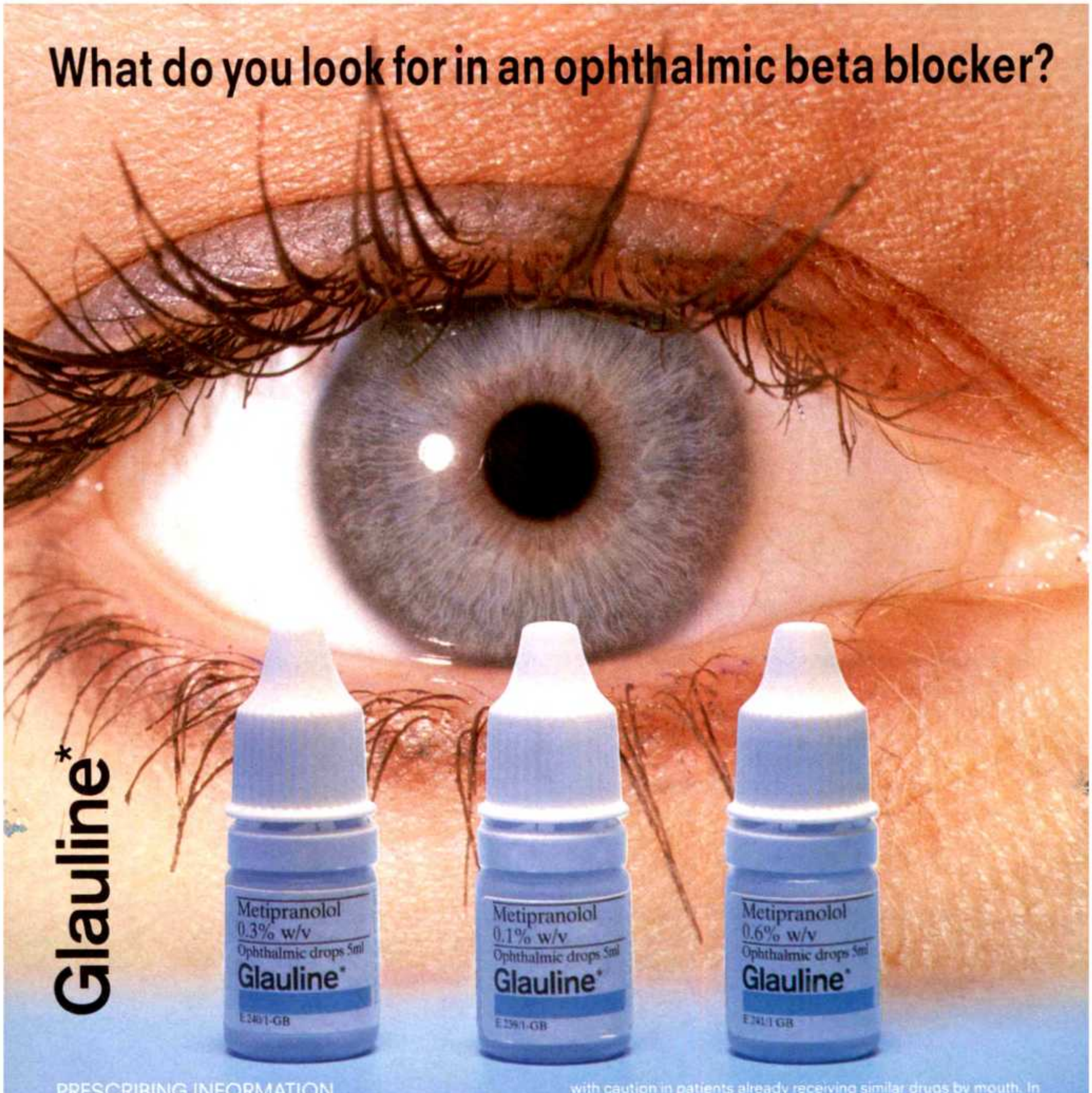

PRESCRIBING INFORMATION

PRESENTATION

A clear, colourless solution in a plastic dropper bottle. Glauline is available in three strengths containing 0.1%, 0.3% or 0.6% w/v metipranolol together with benzalkonium chloride 0.01% w/v as a preservative.

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Glauline is a beta adrenoceptor blocking agent used in the topical treatment of chronic open-angle glaucoma and other conditions in which intra-ocular pressure is elevated above normal levels.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop instilled into the affected eye twice daily. Newly diagnosed patients should be treated in the first instance with Glauline 0.1%, changing to a higher strength if adequate control is not achieved or maintained. Patients on existing therapy, whether or not this is to be continued, should receive 0.3% Glauline and the intraocular pressure of all patients should be monitored regularly (e.g. every 4-6 weeks).

Use of the 0.6% strength is only recommended in patients who are not controlled on the lower strengths of Glauline.

CONTRA-INDICATIONS, WARNINGS ETC.

The use of Glauline is not recommended in patients with obstructive airway disease, cardiac failure or hypersensitivity to metipranolol. Beta blockers should not be given with verapamil and neither drug should be administered within several days of discontinuing the other. As absorption into the circulation is possible, Glauline should only be used with caution in patients already receiving similar drugs by mouth. In particular, care should be taken in patients with sinus bradycardia and greater than first degree heart block. Although there is no evidence to suggest that metipranolol has teratogenic properties, its use during pregnancy should be avoided, unless the potential benefits are considered to outweigh the possible hazards. No clinical trials in children have been carried out. Glauline should not be used in patients fitted with soft (hydrophilic) contact lenses.

PHARMACEUTICAL PRECAUTIONS

Glauline should not be diluted or dispensed from any container other than the original bottle. It is potent for three years unopened, but as with other eye drops the contents of each bottle should be discarded one month after opening.

LEGAL CATEGORY – POM

PACKAGE QUANTITIES

Glauline is supplied as a sterile ophthalmic solution in a 5ml plastic dropper bottle.

FURTHER INFORMATION

Glauline has little or no effect on pupil size or accommodation.

Glauline is generally well tolerated but some patients may complain of a slight stinging which soon passes off. Transient headaches have also been reported.

PRODUCT LICENCE NUMBERS

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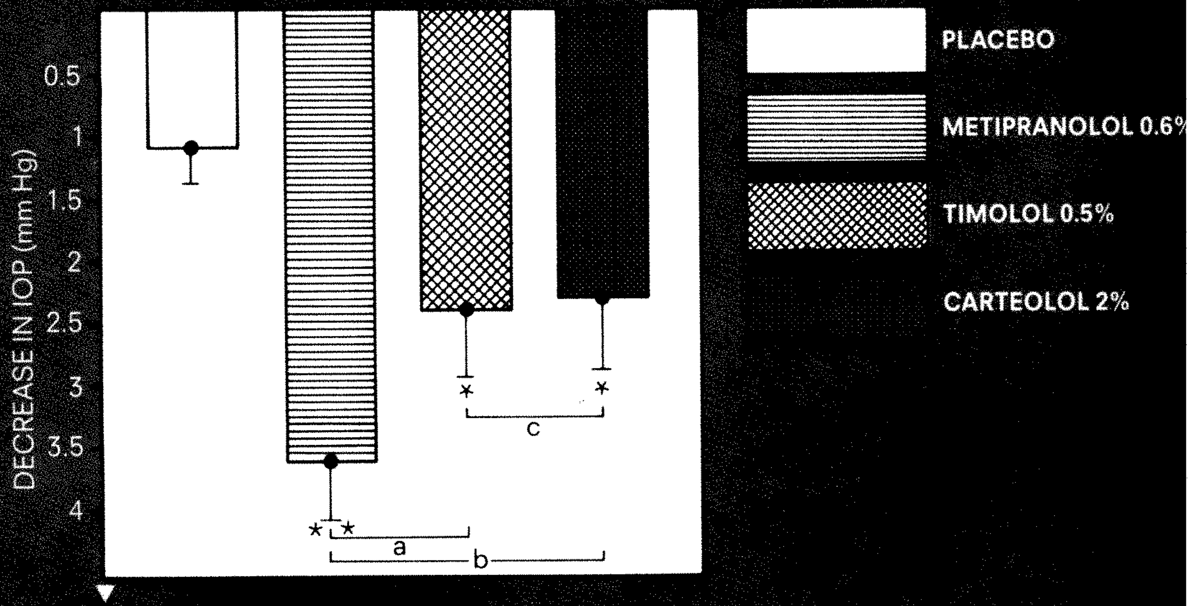
LOWERING OF INTRA OCULAR PRESSURE

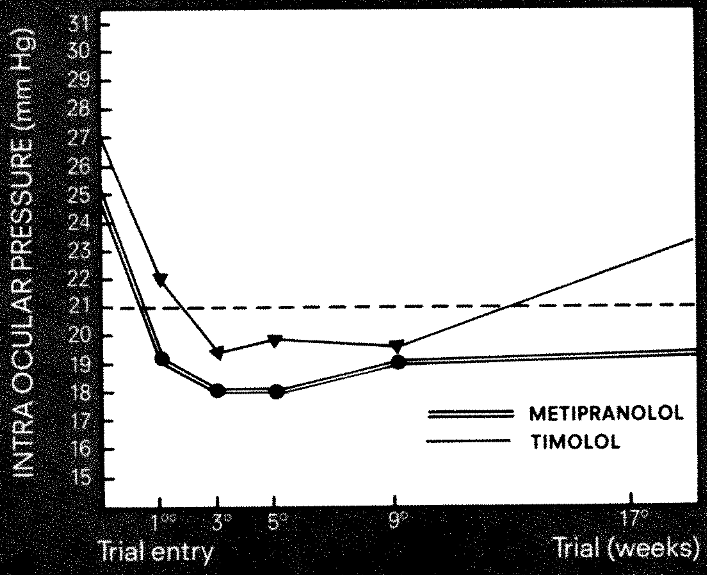
Glauline* has been shown to be more effective than timolol.

(a) In a one drop study[1]



Mean (± SE) decrease in intraocular pressure *(IOP)* after one drop of ophthalmic ß-blocker in each eye. (*$P < 0.01$; **$P < 0.001$ vs. placebo; a, $P < 0.01$; b, $P < 0.01$; c, NS.)

(b) In a middle term study[2]



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British Journal of Ophthalmology, 1989, **73**, 39–41

Repair of an avulsed upper lid and partially severed lower lid

G W AYLWARD AND R OHRI

From the Western Ophthalmic Hospital, Marylebone Road, London NW1 5YE

SUMMARY We present a case in which trauma from a broken glass resulted in complete amputation of the upper lid and severe lacerations to the lower lid but with an intact and functioning globe. The avulsed upper lid was repaired as a composite autograft. The possible management of such an unusual case is discussed.

Case report

A 45-year-old man presented to the Western Ophthalmic Hospital after being assaulted one hour previously in a public house with a broken beer glass. On examination he was found to have multiple lacerations of the forehead and tissues surrounding the right eye. There was a full-thickness defect of the right upper lid involving almost its entire length with a small remnant of margin remaining at the medial and lateral extremities. The defect extended vertically to beyond the upper skin crease, exposing the cornea and sclera to 10 mm from the limbus (Fig. 1).

The missing lid tissue had been recovered intact from the beer glass by the ambulance crew and accompanied the patient in a brown envelope (Fig. 2). There were two full thickness lacerations of the lower lid. One was just medial to the punctum involving the lower canaliculus and extended vertically for 10 mm from the lid margin. The other was 3 mm medial to the lateral canthus and extended 10 mm vertically from the lid margin. This resulted in an extensive flap of intermediate lid tissue which was lying reflected on the cheek exposing the lower fornix. A visual acuity of 6/18 was recorded from the right eye. The cornea was clear and, remarkably, there was no laceration of the globe.

In view of the large defect and consequent exposure of the cornea it was decided to undertake a primary repair using the accompanying lid tissue as a composite autograft. The patient was started on systemic ampicillin 500 mg four times a day, and the severed lid was wrapped in a sterile swab moistened with normal saline and refrigerated. The lower lid flap was brought up to cover the cornea and taped to the brow.

The patient was taken to the theatre four hours later and given a general anaesthetic. The lid tissue was found to fit the defect in the upper lid exactly. It was sutured into place in layers with interrupted 6/0 collagen sutures to the conjunctiva and subcutaneous tissues, and 6/0 black silk to the skin. The lower lid flap was aligned to the free edges and repaired in layers with the same suture materials. The repair of the margin was performed under the operating microscope. No attempt was made to anastomose the severed ends of the canaliculus. Full examination of the globe revealed a small laceration in the lower conjunctiva, but the underlying sclera was intact. There was no intraocular injury apart from a small area of commotio retinae at 6 o'clock. Chloramphenicol ointment was instilled and a firm pad and bandage applied for 48 hours.

Postoperatively the repair looked satisfactory and

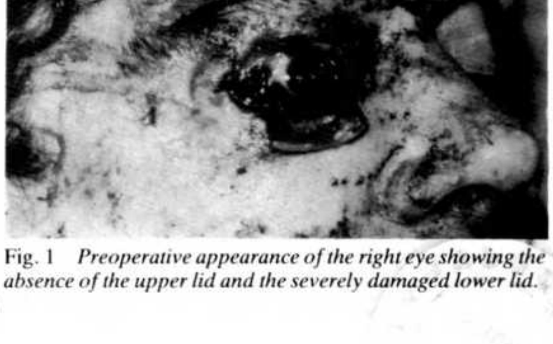

Fig. 1 *Preoperative appearance of the right eye showing the absence of the upper lid and the severely damaged lower lid.*

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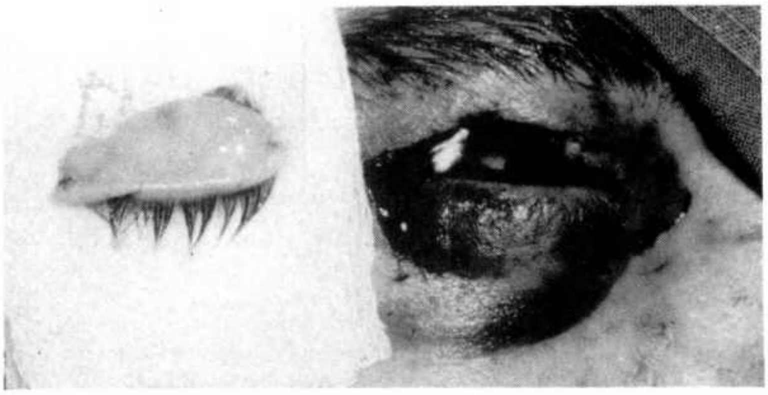

Fig. 2 *The segment of upper lid prior to the autograft.*

afforded good cover for the globe. He was treated with topical chloramphenicol ointment and oral ampicillin 500 mg, both four times a day, for 10 days. Some oedema of both lids developed on the fifth postoperative day, being more marked in the lower lid than the upper. The upper lid oedema settled after 14 days and the skin sutures were removed. On discharge the eye could be opened and closed and there were no signs of corneal exposure.

He was followed up in the outpatient department but unfortunately defaulted frequently. Fourteen weeks after surgery he had occasional epiphora but no discomfort. The margin of the upper lid was retracted and there was loss of cilia. The lower lid was thickened and there was a large ectropion. Figs. 3 and 4 show the eyelids in the open and closed positions respectively one year after surgery. He has reasonable upper lid function with no signs of corneal exposure. The appearance of the lower lid represents a cosmetic problem to the patient, and further surgery is planned to correct this.

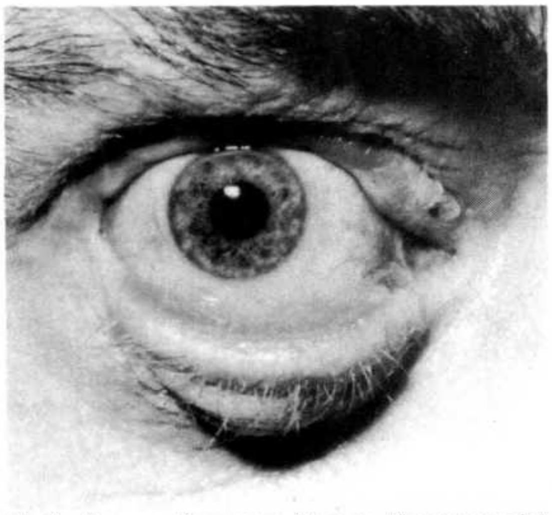

Fig. 3 *One year after surgery; lids open. There is upper lid retraction and loss of cilia. The lower lid is thickened and there is ectropion.*

Discussion

The problems associated with the reconstruction of the upper lid are well described by Mustardé.[1] His recommended method for repair of large defects makes use of a portion of lower lid on a vascular pedicle. The Cutler-Beard technique[2] and the method of Hughes[3] also make use of lower lid. In our case the lower lid was severely injured and the marginal circulation was compromised. We therefore considered that these techniques were not applicable. McGregor described a method using lateral advancement in conjunction with a Z-plasty to relieve tension.[4] However, he recommends it for defects no larger than two thirds of the width of the lid and with portions of tarsal plate either side. A

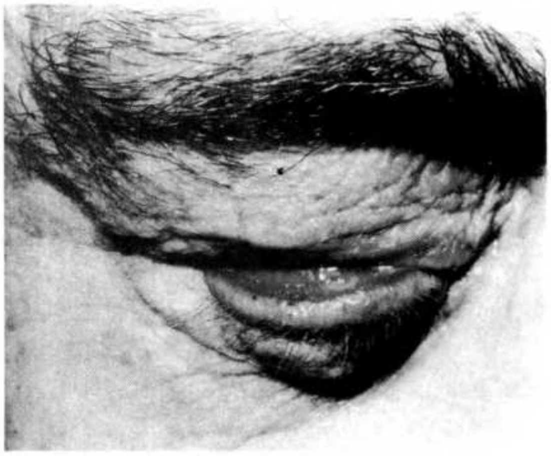

Fig. 4 *One year after surgery; lids closed.*

further technique was suggested by Mustardé[1] as being suitable for the treatment of a case of total loss of both eyelids with an intact eye, though he had not actually seen such a case. It involves suturing conjunctival flaps across the cornea and covering with a midline flap from the forehead, dividing the graft to fashion two lids at a later date. This method was used in a case described by Hay,[5] and similar techniques were used in two cases described by Achauer and Menick.[6]

We concluded that the simplest approach to the immediate management of this case was to suture the severed lid into place as a composite autograft. There was obviously a risk of necrosis, but there were several favourable factors. Firstly, the local blood supply is excellent in this region. Secondly the severed lid fitted the defect exactly, with no missing tissue, so that it could be sutured without tension. Thirdly, the edges appeared to be cleanly cut with minimal contusion. Fourthly the ischaemic time was only five hours, and for four of these the lid was kept moist and refrigerated.

In the event the graft appeared to take well, though there was subsequent loss of cilia and some lid retraction. These complications have been reported recently in a series of five cases of eyelid avulsion due to human bites.[7] All five cases were treated in a similar manner to this case and no necrosis occurred even though one was grafted 26 hours after trauma. Two patients developed lid retraction and loss of cilia. However, this did not occur in those patients who underwent surgery less than 14 hours after trauma.

We thank Miss Sue Ford, of the Western Ophthalmic Hospital, who took and prepared the photographs, and Mr Redmond J H Smith for valuable advice and for allowing us to report on his patient.

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Ocular toxicity of desferrioxamine — an example of copper promoted auto-oxidative damage?

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SUMMARY Three patients with rheumatoid disease were given the 'iron chelating' drug desferrioxamine (DFX), which also has an appreciable affinity for copper. The drug was injected cautiously, in lower doses than in patients with thalassaemia, and intramuscularly to evaluate its anti-inflammatory effects. Two of the three patients developed ocular abnormalities. One patient, who also received methyldopa, developed severe but reversible visual failure associated with an abnormal electro-oculogram (EOG); another showed reversible depression of the EOG. Analysis of the cerebrospinal fluid (CSF) of this patient showed an increase in phenanthroline detectable (non-caeruloplasmin-bound) copper. Analysis of the CSF of the third patient, who did not develop any clinical or electrophysiological ocular abnormalities, was normal. Haematological assessments indicated that all three patients probably had reduced iron stores. With in-vitro systems DFX was shown to mobilise copper from albumin and to facilitate copper movement across a cell membrane model, a property that was enhanced by methyldopa. Our observations are consistent with the concept that in rheumatoid patients low iron stores may result in binding of copper by DFX and that this may be of central importance in causing the ocular toxicity of DFX.

We have described previously details of three patients with rheumatoid arthritis who developed ocular problems after the subcutaneous infusion of desferrioxamine (DFX).[1] In one case DFX was given in conjunction with the phenothiazine, prochlorperazine. This patient lost consciousness, and analysis of his cerebrospinal fluid (CSF) showed a decrease in loosely bound (catalytic) iron He subsequently developed an optic neuropathy and pigmentary retinopathy. This was associated with abnormalities of the electro-oculogram (EOG) and electroretinogram (ERG), the former recovering within 18 months, the latter failing to recover. These disturbances were associated with a rise in CSF non-caeruloplasmin bound ('catalytic') copper, with values becoming normal after seven months. DFX was subsequently shown to act synergistically with prochlorperazine by in-vivo and in-vitro studies. Our results tentatively suggested that DFX alone or DFX in combination with prochlorperazine may have liberated copper, inducing oxidative damage within the neural tissue including retina.[1] We have presented some evidence recently that this may be the case for phenothiazine drugs.[2]

Our clinical studies, which were designed to assess the efficacy of DFX as an anti-inflammatory compound in rheumatoid disease by inhibiting iron-promoted oxidative damage were then stopped. However, following reports by Giordano *et al.*,[3,4] that lower doses of intramuscular DFX (1 g every 14 days) increased the haemoglobin concentration in rheumatoid patients, and apparently suppressed inflammation without 'reported' side effects, ethical committee approval was obtained for continued studies at the lower dosage regimen. We extend the clinical and biochemical studies and describe in-vitro studies that support the case for copper mediated mechanisms of damage in DFX toxicity.

Three cases are presented. Of these one patient who received only 5 g of DFX in conjunction with methyldopa developed marked bilateral retinal oedema, a pigmentary epitheliopathy, and grossly

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abnormal responses to ocular electrodiagnostic tests Another, receiving a total of 14 g of DFX, showed an asymptomatic ocular disturbance detected by electrophysiological testing. Our subsequent in-vitro studies provide further insight into the mechanism of these effects and support the view that the ocular changes can, in principle, result from copper promoted oxidative damage within the interphotoreceptor matrix and retinal pigment epithelium (RPE), with particular damage occurring to the photoreceptor outer segments.

Material and methods

EOG and ERG studies were performed in accordance with the following protocols. The EOGs were recorded by the technique outlined by Arden *et al*[5] ERGs were recorded in scotopic and photopic conditions with Burian-Allen contact lens recording electrodes. All ERGs were obtained by a Ganzfeld stimulus and were averaged with a Nicolet C4 analyser. In order to obtain a rod dominated response the patients' eyes, once dilated, were dark adapted for 15 minutes, and a low-intensity white light was used. A cone dominated response was obtained by light adapting the eyes and then using a 30 Hz red stimulus.

The visual evoked responses (VER) (recorded only in patient 3) were obtained by means of flash and pattern stimulation, with two-channel bipolar recordings, 10/20 system electrode placement. The responses were recorded on a Nicolet C4 analyser. Pattern check sizes were 1°50′, 50′ and 25′.

Phenanthroline copper was measured as described by Pall *et al.*,[6] a modification of the method of Gutteridge.[7] We have established a 'normal range' of 1·5 (0·5) μM (mean, SD) derived from 28 CSF samples from patients with a variety of disparate neurological and orthopaedic conditions.[6] All CSF was collected from the supine patient in the morning with G22 stainless steel disposable needles which we have shown to be free of contamination with copper.

Case reports

PATIENT 1

A 60-year-old (53 kg) man with seropositive erosive, destructive rheumatoid disease, with disseminated and cropping rheumatoid nodules, was admitted to the trial, having been unresponsive to 'second line drugs' and poorly controlled on prednisolone EC 10 mg, and naproxen 500 mg twice daily. His ESR was 30 mm/h C-reactive protein (CRP) 21 mg/l, Hb 15·7 g/dl, ferritin 51 μg/l (normal, >15 μg/l), serum Fe 12·2 μmol/l (normal 11–30), total Fe binding capacity 59·6 μmol/l (normal 45–70) [% saturation 20·5 (normal >15)]. These indices suggested normal iron stores.

In this patient EOGs and ERGs were normal; the EOG being recorded as 170% in both eyes before treatment and 172% in the R eye and 167% in the L eye after treatment. Our normal values for EOG in a rheumatoid population of >50 years are >155%, this value having been obtained from a sample of 65 patients. He received 14 daily intramuscular injections of 1 g of DFX. At the end of the treatment period his ESR was 20 mm/h, CRP 25 mg/l, ferritin 22 μg/l, Hb 13·5 g/dl, serum Fe 6·6 μmol/l, total Fe binding capacity 69·4 μmol/l [% saturation 9·5]. Clinical assessments of disease activity at the end of the trial period and for the subsequent three months showed no significant change from pretreatment values. A bone marrow estimation performed one month after DFX was discontinued showed a complete absence of iron stores: his iron indices were similar to those at the end of the trial period.

PATIENT 2

A 53-year-old woman (60 kg) with seropositive erosive rheumatoid arthritis, without systemic complications, but unresponsive to previous 'second line' therapy with sulphasalazine was admitted to the trial. Her symptoms were poorly controlled on azapropazone. At the onset of the study her ESR was 76 mm/h, CRP 51 mg/l, Hb 13·3 g/dl, ferritin 117·5 μg/l, serum Fe 8·1 μmol/l, total Fe binding capacity 43·8 μmol/l (% saturation 18·5). The patient received 14 daily intramuscular injections of 1 g of DFX Electrophysiological testing during her first week of treatment showed a normal but borderline EOG result (160% L, 154% R) At the end of the treatment period the EOG had, if anything, deteriorated slightly, (152% L, 146% R). Visual acuity, funduscopy, and electroretinography remained normal and unchanged throughout. Three weeks later the EOG was repeated and appeared to have improved (174% L, 160% R). A parallel study on five rheumatoid patients who had a similar number of EOGs carried out over a similar time period showed a maximum variation in the EOG of 16%. We therefore considered that the improvement in the EOG was, at least in the left eye, significant. At the end of the study the patient felt much improved, but no clinical or laboratory index indicated reduction in disease activity. Her indices in all respects were unchanged. A bone marrow examination showed an absence of stainable iron. Follow-up over the next six months has revealed no new side effects or visual disturbance.

PATIENT 3

A 75-year-old woman (45 kg) with seropositive erosive rheumatoid disease with mild Sjögren's syndrome and unresponsive to 'second line therapy' was admitted to the trial. She was taking methyldopa 250 mg per day and bendrofluazide 2·5 mg for mild hypertension, and prednisolone EC 10 mg and diclofenac 50 mg three times a day for the arthritis. At the onset of the study her ESR was 80 mm/h, CRP 92 mg/l, Hb 12·5 g/dl, ferritin 81 µg/l, serum iron 5·3 µmol/l, total Fe binding capacity 62 µmol/l (% saturation 8·5). The EOG prior to treatment with DFX was at the lower limit of our normal range (154% R, 150% L). Visual acuity was 6/6 R and L. She received five 1 g daily intramuscular injections of DFX. Twenty hours after the last injection the patient developed profound visual symptoms, with visual acuity reduced to 4/36 R and counting fingers L. Posterior pole retinal oedema and pigmentary epitheliopathy were diagnosed by fluorescein angiography. The EOG was grossly subnormal (100% R, 86% L—inverted). The ERG revealed normal scotopic responses consistently of higher amplitude from the R eye (530 µV R, 420 µV L, normal=>300 µV). The red flicker ERGs were slightly reduced in the right eye (45 µV; normal>60 µV) and reduced in the left eye (30 µV) but with no delay. This was consistent with the fundus appearance and the grossly impaired visual acuity. The oscillatory potentials of the ERG, reflecting the integrity of the vascular supply to the retina, were normal. VERs revealed reduced amplitudes in both eyes (3 µV R, 2 µV L, normal>4 µV) but no evidence of delay.

All tests were repeated three weeks later. The posterior pole oedema had largely resolved, leaving pigment epithelial atrophy and mottled hyperfluorescence. Visual acuity had improved to 6/6 R and 6/12 L. The EOG had improved considerably (180% R, 150% L). The scotopic ERG had deteriorated to 320 µV R and 240 µV L, left eye responses now being abnormal. However, the flicker ERG had improved to within normal limits (74 µV R, 66 µV L). The VER had also improved (6 µV R, 5 µV L) to normal. A final assessment seven weeks after the visual episode revealed no change in the EOG or scotopic ERG, but the VER and flicker ERG had further improved. Visual acuity was recorded at 6/6 R and 6/9 L. From our test protocol the ERG changes suggest a deterioration of rod function but an improvement in cone function. A bone marrow biopsy was performed two weeks after the DFX had been started and showed only occasional small Perls-positive iron fragments in the reticuloendothelial meshwork. At this stage her serum iron, total iron binding capacity, and ferritin were unaltered from baseline values

Table 1 *Desferrioxamine-induced copper removal from albumin*

Time (h)	*Copper (ng/ml)*		
	Desferrioxamine	*Desferrioxamine +methyldopa*	
0·5	12 (0 5)	19 (2)	p<0 02
2	14 (1)	16 (2)	NS
7	19 (1)	20 (4)	NS

Albumin and transferrin (plasma concentrations) were incubated in HEPES (80 mM, pH 7·4) containing HCO^{3-} (27 mM), copper (100 ng/ml), and iron (3 3×10^{-6} M) for 18 h Desferrioxamine (10^{-3} M) in the presence and absence of methyldopa (10^{-4} M) was added, and aliquots (2·5 ml) were removed at different times and filtered with an Amicon YM5 membrane (5000 molecular weight cut-off) The filtrate was analysed for both iron and copper (n=4) by atomic absorption spectrophotometry Results are expressed as the mean of four determinations (SEM in parentheses).

CSF STUDIES

At the time our third patient developed ocular symptoms, patients 1 and 2 had received 14 intramuscular injections (the maximum to be given under the protocol). Patient 1 had suffered no side effects, but patient 2 had developed an abnormal EOG. The ocular side effects, occurring in patient 3, were discussed with the two other patients. In view of our previous experience[1] we were interested in establishing whether loosely bound, non-caeruloplasmin-bound copper with the capacity to induce oxidative damage (phenanthroline copper) was altered in any of these patients' CSF. CSF has many features in common with aqueous humour, and we reasoned that what happened in one fluid may also happen in the other. After discussion patients 1 and 2 agreed to a lumbar puncture examination; it was considered unreasonable to request this investigation from patient 3, as she was elderly and distressed by her visual loss. Patient 1, without ocular problems, had a normal Cu concentration (1·8 µM) (normal 1·5 (0·5) µM (mean, SD)). In patient 2, with an abnormal EOG, the Cu level was considerably raised (3·4 µm). No correlation has been found between CSF loosely bound copper and age or sex in any of the groups studied so far.[6]

CHEMICAL CONSIDERATIONS

Although DFX is generally considered to be a specific iron (III) chelator, it has an appreciable affinity for copper (II) (affinity constant 10^{31} for Fe(III); 10^{14} for Cu(II),[8] particularly under physiological conditions where a number of endogenous high affinity iron (III) binding sites will compete with DFX for the limited iron pool. In an attempt to assess the ability of DFX to scavenge copper under conditions similar to those found in human plasma DFX was incubated with a solution of albumin and transferrin (30% saturated with iron) at physiological concentrations. DFX mobilised a significant proportion of the added copper (15% after 2 hours, Table 1); indeed proportionally more copper than iron was chelated by DFX, under these conditions. Interestingly, the inclusion of methyldopa, which patient 3 had received during the trial, in this system increased the rate of exchange of copper between albumin and DFX (Table 1). Thus a possible cause of synergism between DFX and methyldopa is the enhanced mobilisation of plasma copper.

Methyldopa, by analogy with most substituted catechols, is capable of chelating copper (II),[9] forming highly water soluble complexes which will not permeate membranes as rapidly as the copper-DFX complex. Thus under conditions of high local methyldopa concentrations DFX-induced elevated copper levels could have prolonged lifetimes. This possibility was invesigated by means of Pressman cells. We previously showed that DFX can facilitate the movement of iron across non-aqeuous phases.[1] In this study we show that DFX can also facilitate copper movement (Fig. 1) However, methyldopa, when present at a concentration equimolar with that of DFX, inhibits this translocation process, presumably by forming a water soluble copper complex. Thus a second interaction between DFX and methyldopa, centred on the ability of both drugs to co-ordinate copper, is also possible.

Discussion

Despite suggestions that DFX is efficacious in low dosage in patients with rheumatoid arthritis and is without 'reported' side effects,[3] our results clearly indicate that even at this dose the therapeutic index is too low to justify further use in such patients. Our results also support the view that toxicity is related to the level of iron stores.[8] Quite apart from considerations of age, the differences in iron stores between patients with rheumatoid arthritis and those with thalassaemia may explain the apparent higher risk of toxicity in the former group. It is of interest that in patients with β thalassaemia who also develop neuro-ophthalmic symptoms despite high iron stores[9] DFX increases urinary copper excretion.[11] Furthermore, the results highlight the difficulty in assessing iron stores in a rheumatoid population from assessments of serum ferritin, serum iron, and iron binding capacity. We and others have suggested that a serum ferritin >50 μg/l implies adequate iron stores in the presence of inflammation;[12,13] this appears to be incorrect. It is clear that both of our patients who developed ocular lesions had reduced iron stores, though the one patient who did not was also probably iron depleted. Our in-vitro data (Table 1, Fig. 1) suggest that in such circumstances, when transferrin is not saturated, DFX will chelate copper and has the potential of translocating this metal across membranes. The additional observation that methyldopa has the potential of interacting synergistically with DFX, both in plasma to release copper and in cells to trap copper, offers an explanation for the accelerated development of severe toxicity in patient 3 and bears analogies with the interaction of DFX with prochlorperazine that we have reported previously.[1]

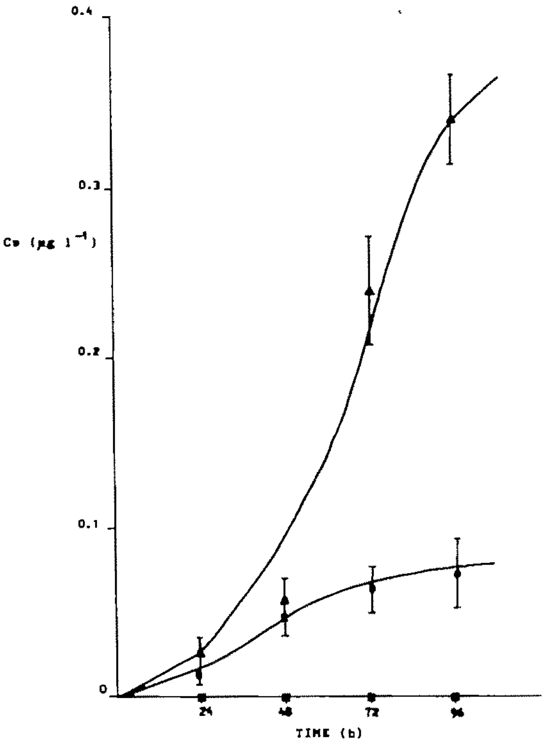

Fig. 1 *The rate of copper movement through a chloroform phase as catalysed by the presence of desferrioxamine. A Pressman cell was constructed such that chloroform (6 ml) separated two aqueous compartments A and B (6 ml MOPS, 20 mM, pH 7·4). The two aqueous solutions were continuously stirred mechanically. Copper (II) nitrilotriacetate (1 mg/l^{-1} copper, 10^{-4} M NTA) was added to side A Samples were taken from side B every 24 h and analysed for copper by atomic absorption spectrophotometry ●, desferrioxamine (1 mM) added to side B; ▲, desferrioxamine (1 mM) added to side B and methyldopa (1 mM) added to side A; ■, no addition to either side A or B. All the results are the mean of at least three individual determinations±SEM.*

The most significant ocular electrophysiological finding in our patients were the disturbances in the EOG. In patient 3 these rapidly became subnormal and then quickly improved. The origin of the EOG, a test which has been used for monitoring chloroquine toxicity among other conditions remains a debated subject. It is reported that the electro-ocular potential originates between the RPE and the external limiting membrane and is due to potassium ion fluxes across the RPE cell membranes,[14 15] the light response being due to a slow depolarisation of the basal cell membrane of the RPE. Our data, when coupled with our previous observation, strongly suggest that the copper detectable by the 'phenanthroline copper' assay, which would include desferrioxamine-bound copper, might directly or indirectly change the ionic potential across the RPE, causing a reduced electro-ocular potential rise during light stimulation and hence a low EOG. The retinal pigment epithelium appears to have good powers of recovery from such an insult, as no lasting changes to the EOG occurred.

In patient 3 the electroretinogram started to deteriorate to low intensity scotopic (rod) stimulation while the EOG and red flicker (cone) ERG was recovering. It remained reduced even when the EOG and flicker ERG had completely recovered. The electroretinogram assesses the functional integrity of the outer two-thirds of the retina, including rod and cone function. We presume from this observation that oxidative damage has now occurred in the rod outer segments, while the cone cells recovered in line with the resolving pigment epitheliopathy. Rapp and Williams[16] and Organisciak and Noell[17] have reported that light-induced oxidative damage is a function of rhodopsin content and opsin packing density in photoreceptor outer segments. In patient 3 it is possible that, despite the cones' recovering from the oxidative insult, the rod outer segments had suffered injury due to the combined effects of Cu and light damage. Certainly the time scale from the start of the oxidative damage of the cones to the induction of oxidative damage to the rods would correlate with the animal model findings of O'Steen and Donnelly,[18] who found that the oxidative effects of light damage take several days before they are fully expressed. The current evidence suggests that the EOG should be carefully monitored during treatment with DFX.

Our data suggest that copper fluxes induced by DFX are important in mediating its ocular toxicity and that these fluxes may be exacerbated by methyldopa. Copper probably has an important role in retinal physiology, being found in high concentrations within the RPE,[19] a site which is known to be affected by DFX.[20] The molecular consequences of DFX-induced copper translocation are unknown but there are numerous possibilities:

(1) Decompartmentalised copper may induce oxidative cell membrane damage via a process of lipid peroxidation which it is known to stimulate in vitro.[21] Products of lipid peroxidation are known to be toxic to retinal photoreceptor cells.[22 23] The abundance of highly poyunsaturated fatty acids within the retina would predispose to such a process of lipid peroxidation.

(2) Movement of copper into extracellular fluids may interrupt monoaminergic neurotransmission in the retina—copper playing an important part in the synthesis of both dopamine and noradrenaline for example. The activity of the rate-limiting enzyme for dopamine biosynthesis, tyrosine hydroxylase, is reduced in states of copper deficiency, and dopamine β hydroxylase, which converts dopamine to noradrenaline, is a copper-dependent enzyme.[24]

(3) Synthesis of the potential antioxidant, neuromelanin,[25] may be impaired by reduction of the activity of tyrosinase, another copper-containing protein. This may also predispose the subject to increased oxidative damage.

(4) Increased concentrations of low-molecular-weight/loosely bound copper ions in various subcellular locations may inhibit the activities of many molecules, including enzymes and catecholamines, possibly by promoting oxidative damage.[26 27]

Although the molecular mechanism whereby DFX toxicity is mediated remains uncertain, we have presented prima facie evidence that the chelation of copper is essential to this process. It follows that the interactions between copper, iron, and DFX and other metal ligating agents such as methyldopa may, among other factors determine an individual patient's susceptibility to the ophthalmic toxicity of DFX

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Idiopathic presenile cataract formation and galactosaemia

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SUMMARY Five hundred patients undergoing cataract surgery were prospectively examined, and 46 Caucasian patients were found to have strictly idiopathic cataracts severe enough to warrant surgery on or before age 55. In a masked fashion we determined the activity of galactokinase (GK) and galactose-1-phosphate uridyl transferase (GPUT) in these patients as well as on 53 age matched controls. With respect to GK no cataract patient had an enzyme level of less than 2 standard deviations below the control mean. However, 3 of 45 (6·7%) patients in the cataract group had a GPUT level less than 2 standard deviations below the mean for controls, and were presumably heterozygotes for this enzyme. In comparison with the expected population rate of 0·8% this is highly significant (p=0·006). Abnormalities in galactose pathway enzymes may therefore predispose to development of presenile cataracts. In affected people there is a possibility of treating these patients clinically by dietary restriction of dairy products or by using aldose reductase inhibitors to prevent or reverse cataract formation.

Galactosaemia is an inborn error of metabolism characterised by inability to metabolise galactose due to absence of galactose-1-PO_4 uridyl transferase (GPUT) or deficiency or absence of galactokinase (GK) (Fig. 1). Cataract formation is a primary manifestation in both enzyme defects.[1] However, classic galactosaemia is fatal unless galactose is withdrawn from the diet in early life.

Kinoshita[2] and Cogan *et al.*[3] have shown that cataract formation in galactosaemia is due to the accumulation of dulcitol through the action of the enzyme aldose reductase (AR) (Fig. 1, reaction 4). The polyol dulcitol does not readily pass through cell membranes and thus accumulates within lens fibres, including osmotic swelling. Subsequently there is severe derangement of metabolic activity, resulting in loss of amino acids, alteration of protein synthesis, changes in membrane permeability, and depression of adenosine triphospate (ATP) and reduced glutathione (GSH) levels. Finally fibres swell and rupture, resulting in cataract formation. Recent studies also suggest that oxidative damage due to competition between aldose reductase and glutathione reductase for nicotinamide adenine dinucleotide phosphate (NADPH) may be another contributing factor in galactosaemic cataractogenesis.

Recently, potent aldose reductase inhibitors became available and were used as biological probes to determine the role of AR in galactosaemia and diabetes. It was found that galactose-induced cataracts in rats can be completely prevented by systemic treatment with sorbinil, a potent AR

$$1.\ \text{Galactose} + \text{ATP} \xrightarrow{\text{Galactokinase}} \text{Galactose-1-phosphate} + \text{ADP}$$

$$2.\ \text{Galactose-1-phosphate} + \text{UDP glucose} \xrightleftharpoons[\text{uridyl transferase}]{\text{Galactose-1-phosphate}}$$

$$\text{Glucose-1-phosphate} + \text{UDP galactose}$$

$$3\ \text{UDP galactose} \xrightleftharpoons{\text{UDP galactose-4-epimerase}} \text{UDP glucose}$$

$$4\ \text{Galactose} + \text{NADPH} \xrightleftharpoons{\text{Aldose reductase}} \text{Dulcitol} + \text{NADP}$$

Fig. 1 *Galactose metabolic pathway.*

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inhibitor.[4] Subsequently it was shown that systemic and topical application of sorbinil can reverse cataracts in galactosaemic animals.[5] Interestingly new experiments have also shown that AR may be involved in other tissues, such as nervous, vascular (including retinal vessels), corneal, and renal tissues.[3]

Heterozygotes for GK deficiency have approximately half the enzyme activity in the erythrocytes.[6-8] It was suggested that heterozygotes may be prone to early cataract formation. It has been estimated that GK heterozygosity occurs in 0·2% of the population and GPUT heterozygosity in 0·8% of the population.[9 10] A study of patients with presenile cataracts found approximately half of the patients to have abnormalities in the galactose metabolic enzymes.[9 11] Recent studies[12 13] have also shown a high prevalence of GK deficiency heterozygosity in patients with presenile idiopathic cataract.

Thus in many of the idiopathic presenile patients there may be an abnormality to metabolise galactose and hence predispose to cataract formation through the involvement of aldose reductase. The possibility exists of treating these patients clinically by restricting their dietary intake of dairy products or using aldose reductase inhibitors to prevent or reverse cataract formation.

We therefore undertook a case control study at the Wilmer Institute to determine the prevalence of abnormalities in the galactosaemic enzymes in patients with presenile cataract undergoing cataract surgery.

Material and methods

Five hundred consecutive patients scheduled for cataract surgery in the Wilmer Eye Institute Resident Service and those scheduled by two anterior segment surgeons (WJS and AEM) of the Wilmer Eye Institute of Johns Hopkins Hospital were carefully screened.

Inclusion criteria for this study were as follows: (1) Cataract surgery should have been performed or scheduled on or before age 55. Since we used a strict definition of severe cataract requiring surgery by age 55, we increased our age limit to 55, as Stambolian *et al.*[13] did in their study. (2) Patients should come from within a radius of 100 miles from Baltimore. We wanted to limit the geographical area of the study in an effort to make our population geographically homogeneous.

Exclusion criteria were as follows: (1) Patients with a history of diabetes, treatment with corticosteroids, uveitis, ocular trauma, ocular radiation, myotonic dystrophy, lens subluxation, glaucoma, or congenital cataracts were excluded. (2) Black patients were excluded from the study. It cannot be assumed that reduced GK activity in a black person implies defect heterozygosity, since Tedesco and coworkers[14] reported low GK levels in black patients in the absence of any cataract.

A control population was selected that matched the age, sex, race, and geographical characteristics of the cataract group. Patients with diabetes or myotonic dystrophy were excluded from the control group. Each control subject was screened for the absence of cataract. In general the control group consisted of patients from the Wilmer emergency room, friends and spouses of the cataract group, physicians, and hospital employees.

After obtaining verbal consent, venous blood was obtained from all cataract patients and controls by means of a sterile 7 ml tube containing edetic acid (EDTA) (Vacutainer, lavender stopper, Becton-Dickinson, Rutherford, NJ). 0·1 ml of 50% dextrose in water was added to each sample immediately after collection in sterile fashion. The samples were labelled with the subject's name and date of collection and immediately stored at 4°C. The samples were shipped on wet ice to the laboratory so as to arrive within five days of collection. Each shipment contained samples from cataract patients and control subjects. Laboratory staff performing the assays did not participate in specimen collection, nor did they know which specimens were from the cataract group and which were from the control group.

Erythrocytes were isolated by filtration through an alpha-cellulose and microcrystalline cellulose column.[15] Assays for erythrocyte GK and GPUT activity were performed according to the methods of Beutler.[16] Because of laboratory error occasional assays were ruined, but they could not be repeated. These values were necessarily omitted from analysis. Data analysis was performed at the Wilmer Biostatistical Center.

Results

Five hundred cataract patients of appropriate age, race, and geographical location were screened to yield the study group. Most of these patients did not have 'idiopathic' cataracts. Of the patients that satisfied the study group criteria none refused to participate. However, seven could not be contacted, and four could not come in for venepuncture in accordance with the time constraints of the study. Forty-six patients with presenile idiopathic cataracts were entered into the study. Twenty-four (52%) were male. The average age (SD) was 46 (5·61) years with a range of 32 to 58. The 58-year-old had undergone cataract surgery at age 55 for one eye. Twenty-four (52%) of the patients were aged 50 or

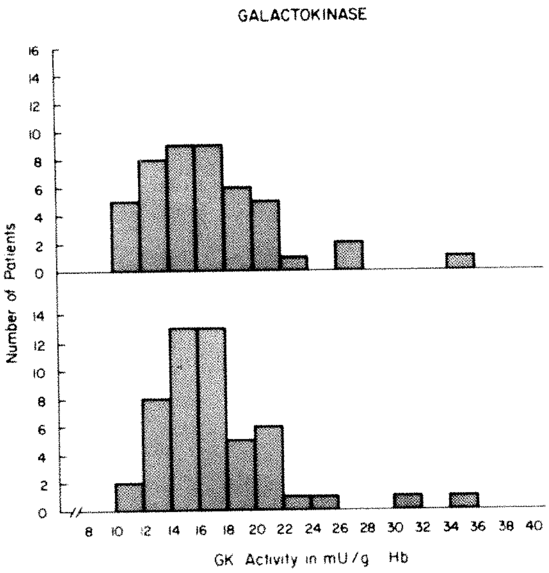

Fig. 2 *Erythrocyte galactokinase activity for control and cataract groups. Cataract group: n=46, mean=16·80, SD=4·61. Control group: n=51, mean=17·55, SD=4·42.*

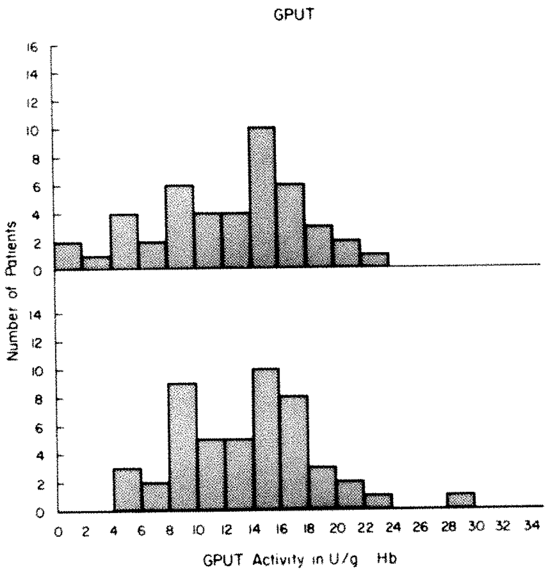

Fig. 3 *Erythrocyte GPUT activity for control and cataract groups. Cataract group: n=45, mean=12·75, SD=5·43. Control group: n=49, mean=13·75, SD=4·89.*

younger at the time of venepuncture. Forty-four of the patients (96%) had bilateral cataracts. Of the 90 cataracts 78 (87%) had a posterior subcapsular opacity and 7 (8%) did not. The type of cataract was unknown in 5 (5%). Family history of cataract was very positive in 22 patients (48%), equivocal in 4 (9%), negative in 19 (41%), and unknown in 1 (2%).

The average duration of symptoms at the time of cataract surgery or examination was three years, with a range of three months to 11 years.

The control population consisted of 53 individuals, 31 (58%) male and 22 (42%) female. The average age of the control population was 44·4 (SD 6·6) years with a range of 30 to 55.

While the average age of the control population was younger than that of the cataract group, a linear regression of GK and GPUT activity versus age for the control group produced slopes of only 0·061 and −0·077 (p=0·50) respectively. Since the control group enzyme activities do not significantly vary with age, this rather small difference in age between the control group and cataract group does not affect comparison between them.

Galactokinase activity determinations were performed on 46 cataract patients and 51 controls. These results are graphically depicted in Fig. 2. The average activity for GK in the cataract group was 16·80 (4·61) mU/g Hb, while in the control group, the value was 17·35 (4·42) mU/g Hb. There is no statistically significant difference between these averages (p=0·60). No cataract patient had a GK activity that fell below 2 standard deviations from the average control value.

GPUT activity was determined on 45 cataract patients and 49 controls. These results are shown in Fig. 3. The average GPUT activity for the cataract group was 12·75 (5·43) U/g Hb. This did not statistically differ from the control average of 13·75 (4·89) U/g Hb (p=0·93). However, three of the 45 cararact patients (6·66%) had a GPUT activity that fell below 2 standard deviations from the control group average, which is a significantly high percentage of abnormals, given the population rate of 0·8% (p=0·006, Poisson probability).

Discussion

True idiopathic presenile cataracts are relatively rare, and this parameter must be carefully monitored by an investigator attempting to study this population. Although our screening population included children, none had idiopathic cataracts. The cataracts were either congenital, traumatic, or associated with other ocular diseases. Children, if they do have galactosaemia, are more apt to be homozygous, not heterozygous. Thus one would not expect them to appear in the cataract group in this study.

The comparison of concurrent controls was also important in this particular study, since the estimated gene frequency of either GK or GPUT enzyme defect in the general population is extremely low. One would not expect the mean value of either enzyme to be different from the controls' unless heterozygotes made up a large part of the cataract group. However, the fact that the percentage of heterozygotes was insufficient to make the mean enzyme levels significantly lower than those of the controls in either group does not exclude the role of GPUT levels in the aetiology of idiopathic cataracts.

In this study no cataract patient had GK levels less than 2 standard deviations below the mean for controls. These results are contrary to the findings of Skalka and Prchal[9,11] and Stambolian *et al.*,[13] who reported, respectively, 37% and 7–8% patients with galactokinase activity more than 2 standard deviations below the avarage. This negative result, given the 0·2% frequency for the heterozygote, is not unexpected and may easily reflect small sample size. However, in agreement with earlier investigators there were 6·7% patients (three out of 45) in the cataract group with significantly low GPUT levels. Although we did not find GK deficiency in our presenile cataract patients, the deficiency of GPUT strongly suggests a role of galactose pathway enzymes in the aetiology of idiopathic cataracts and supports previous work.[9,12,13]

Hence in dealing with patients with idiopathic presenile cataracts it may be worth exploring the role played by the galactose pathway enzymes. Once affected individuals are identified, they and their families may benefit from restriction of dairy products in the diet and possibly from treatment with aldose reductase inhibitors.

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Conjunctival involvement in cicatricial and bullous pemphigoid: a clinical and immunopathological study

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SUMMARY Patients with bullous pemphigoid were found to have significant ocular abnormalities. In a group of 18 patients one had conjunctival shrinkage, and 11 of 15 (73%) had positive linear direct immunofluorescence on conjunctival biopsy from a clinically uninvolved site. Our ocular findings in a group of 14 with cicatricial pemphigoid are also reported and compared with those from a control group of 20. Our findings suggest there is overlap between the pemphigoid groups and raise further questions about the pathogenicity of immunoreactants within the basement membrane zone. Bulbar conjunctival biopsy was simple and well tolerated, and the rate of immunofluorescence positivity of conjunctiva was twice that of skin in both pemphigoid groups.

The acquired subepidermal blistering (pemphigoid) dermatoses have been classified according to both clinical and pathological criteria,[1 2] but in practice this classification is not clear cut. Cicatricial pemphigoid (CP, also known as benign mucous membrane pemphigoid) affects chiefly the mucous membranes, where scarring in the eye or mouth is a necessary feature.[2-7] Skin involvement is found in up to one-third of patients; it also tends to produce scarring but is rarely a major feature. By contrast, bullous pemphigoid (BP) is a non-scarring disease affecting chiefly the skin: mucosal involvement has been reported in the mouth[8] but not previously in the eye. Immunopathological studies in the two disorders also suggest overlap. Tissue direct immunofluorescence (IMF) shows binding of immunoreactants to the basement membrane zone (BMZ) in a linear pattern in both groups.[8-19]

Although conjunctival involvement, both clinical and immunopathological, has been well characterised in CP, it has not previously been reported in BP. We examined the eyes of 18 patients with BP looking for both clinical and immunopathological abnormalities. We report a comparison with 14 CP patients and controls.

Patients and methods

PATIENTS

Patients were recruited from the dermatology and oral surgery departments and so were not known to have conjunctival involvement at the initial identification. They were defined as CP or BP as follows: if the disease affected predominantly the mouth or unequivocal skin scarring was found, the patients were defined as CP. If the skin was chiefly involved, without scarring but with positive direct IMF in skin at some stage of their illness, they were defined as BP.

The duration of disease in the pemphigoid patients varied from 19 years to 2 weeks, average 42 months. 30% were in clinical remission and 50% on systemic treatment at the time of biopsy. Fourteen patients with CP were assessed clinically, and conjunctival biopsies were obtained in 13, eight of whom also had biopsies of skin and oral mucosa. In the BP group the figures were 18, 15, and 11 respectively.

As the study was critically concerned with evidence of conjunctival signs, a group of 20 age matched controls, drawn from routine preoperative patients (cataract, squint, and retinal surgery) were assessed similarly, though their status was not masked. A further seven control patients consented to conjunctival biopsy at the time of surgery.

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No patient, including controls, had a past history of confounding eye disorder known to cause conjunctival scarring, such as injury, infection, atopy, or topical or systemic medication.

CLINICAL ASSESSMENT

The patients were assessed by an ophthalmologist (PF), who was unaware of their status (except of control patients), for full ocular history and examination including slit-lamp microscopy and conjunctival biopsy. They were asked about symptoms such as discomfort, redness, or itching of the eyes, and whether this was of mild, moderate, or severe degree. Slit-lamp examination at 16× magnification was carried out particularly to look for fine linear scarring of the tarsal conjunctiva, which might suggest early involvement in a cicatrising process. This was graded, according to a protocol, as just detectable, definite, moderate, or marked. Scarring with adhesions between tarsal and bulbar conjunctiva (symblepharon) was also looked for by simple eversion of the lids and the depth of the inferior fornix and presence of forniceal folds noted. The bulbar conjunctiva was assessed for clinical signs of active inflammation in terms of vascular dilatation, chemosis, and thickening.

CONJUNCTIVAL BIOPSY

Conjunctival biopsy was taken from a standard site in the upper temporal bulbar conjunctiva (thus from a clinically uninvolved site), using surface anaesthesia with oxybuprocaine drops. With slit-lamp viewing a 2 mm snip biopsy was taken which was embedded in optimal cutting temperature (OCT) medium and snap frozen in liquid nitrogen. Topical chloramphenicol ointment was applied to the eye for five days. Stitching was not necessary. Care was taken to do a biopsy prior to the use of topical fluorescein. Control specimens of conjunctiva were taken from seven patients at routine surgery (cataract, squint, or retinal) from the edge of the surgical incision and processed in the same way.

OTHER TISSUE BIOPSIES

Skin and oral mucosal biopsies were taken by punch technique with local anaesthesia from clinically uninvolved standard sites on the lower lip and volar forearm, and processed and examined in the same way.

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Cryostat sections of the biopsy were prepared and were exposed to fluorescein isothiocyanate (FITC) labelled preparations of antihuman IgG, A, M, C3, C4, and C1q (Hoechst UK Ltd). The sections were examined with ultraviolet light for any fluorescence. Control sections for indirect immunolfluorescence (IMF) were prepared with unlabelled antibodies as blocking agents. The assessing pathologist (PM) was unaware of the patient's status

Results

The ocular findings from 14 patients with CP and 18 patients with BP, compared with 20 control patients, are summarised in Table 1.

In our control group, matched for age, 40% reported minor ocular symptoms. Definite fine conjunctival scarring was found in 45%, and mild bulbar conjunctival chemosis and reddening were common. Conjunctival IMF showed only non-linear staining with IgA within some of the surface epithelial cells in 71% of seven control biopsies.

In the CP group one patient with recent onset of severe mouth ulceration had troublesome eye symptoms, with moderate discomfort of both eyes, and had noticed mild redness and stickiness of the right eye only. She had moderately reddened and chemosed conjunctiva and focal lower tarsal conjunctival ulceration in the right eye only. She did not show ocular scarring, and seemed to be an early presentation of CP simultaneously involving mouth and eyes. Otherwise, conjunctival signs in the CP group were not reliably correlated either with symptoms or with IMF findings, including the presence of

Table 1 *Ocular findings in cicatricial and bullous pemphigoid and control patients*

Clinical diagnosis (no of patients)	*Clinical findings*				*Immunopathological findings*		
	Age in years, average	*Ocular symptoms* %	*Linear tarsal scarring* %	*Conjunctival shrinkage or symblepharon No. of patients*	*Linear deposit at BMZ*		*Non-linear intraepithelial* %
					No	%	
CP (14)	65	62	28	2	13	46	77
BP (18)	74	56	39	1	15	73	67
Control (20)	61	40	45	0	7*	0*	71*

*Obtained from seven separate control patients

Table 2 *Immunopathology of conjunctival biopsies in cicatricial and bullous pemphigoid and control patients*

Clinical diagnosis (no. of patients)	*Linear at BMZ (%)*				*Non-linear intraepithelial (%)*			
	IgG	*IgA*	*IgM*	*C3*	*IgG*	*IgA*	*IgM*	*C3*
CP (13)	5 (38)	1 (8)	0	3 (23)	0	10 (77)	3 (23)	0
BP (15)	8 (53)	0	0	7 (47)	0	11 (73)	0	0
Control (7)	0	0	0	0	0	5 (71)	1 (14)	0

C4 and C1q were negative in all specimens.

C3. Definite fine linear scarring was found in the lower tarsal conjunctiva in four (28%), which was no higher than in the control group. Symblepharon was found in two asymptomatic CP patients (14%). If fine linear scarring was included as a significant feature, evidence of a cicatrising conjunctival disorder was found in six patients (43%).

In the CP group conjunctival IMF showed a positive linear pattern at the BMZ in six of 13 patients biopsied (46%). Two patients showed IgG alone, one patient C3 alone, two patients both IgG and C3 together, and one patient IgG and IgA together. IgA was also found in a non-linear pattern, as in controls, within some of the epithelial cells in 77% (Table 2).

In the 18 patients classified as BP minor clinical symptoms were reported by 56%. No patient had troublesome symptoms. Definite fine tarsal conjunctival scarring was seen in 39% as a non-specific finding. However, one patient had loss of inferior forniceal folding, with shrinkage of the lower conjunctival sacs bilaterally, though there was no focal symblepharon (Fig. 1).

Conjunctival IMF in the BP group showed linear deposition of immunoreactants at the BMZ in 11 of 15 BP patients biopsied (73% positive). Four of these showed IgG alone (Fig. 2), three C3 alone, and four both IgG and C3 together (Table 2).

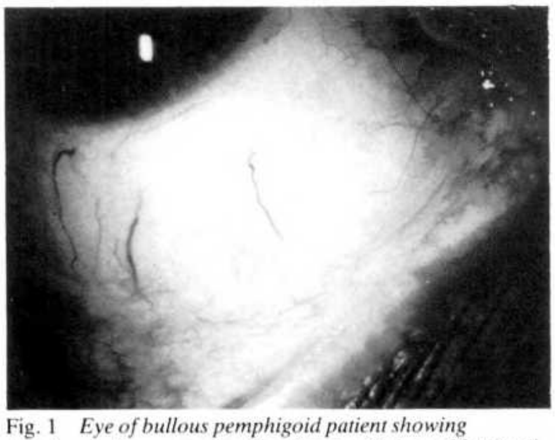

Fig. 1 *Eye of bullous pemphigoid patient showing shrinkage of lower conjunctival fornix with loss of forniceal folding.*

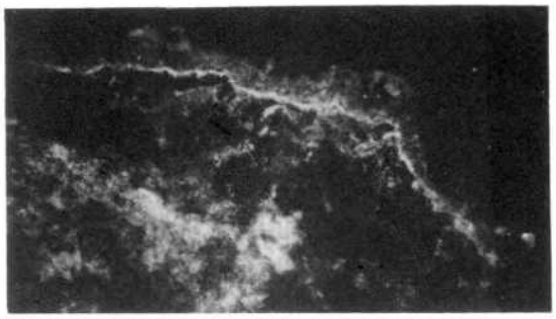

Fig. 2 *Conjunctival direct immunofluoresence in bullous pemphigoid showing linear IgG deposition along basement membrane zone.*

Table 3 summarises the prevalence of positive linear IMF in the three different tissues biopsied in eight CP and 11 BP patients.

Thus overall conjunctiva yielded the highest rate of positive IMF in both CP and BP patients, with over double the rate found in skin in both groups despite initial presentation in skin or mouth rather than the eye.

Discussion

Previous studies have reported clinical[1-8] or immunopathological[9-22] conjunctival features of the pemphigoid groups, but no single study has looked systematically at both features in skin, mouth, and eye. Deposition of immunoglobulins or complement in a linear pattern at the BMZ appears to be specific for these groups.[16 22]

The features of the conjunctival cicatrising disorder in CP have been described[3-7] and distinguished from those found in other disorders. Wright[5] describes three groups of features which may overlap. Acute appearances are conjunctival injection with ulceration which stains with fluorescein. One of our patients presented with this pattern. Intact blisters are rarely seen, though the patient may report them. Advanced disease shows symblepharon, which may be accompanied by sicca, lid deformity, trichiasis,

Table 3 Cicatricial and bullous pemphigoid: positive linear direct IMF at BMZ in three different tissues

Clinical diagnosis (no. of patients)	*% Positive linear direct IMF at BMZ*		
	Conjunctiva	*Lip mucosa*	*Skin*
CP (8)	46	40	20
BP (11)	73	52	37

and secondary corneal changes. There is a further group, often asymptomatic, with less obvious scarring of symmetrical conjunctival forniceal shrinkage, and loss of normal canthal architecture.

We observed fine linear scarring, usually of the central lower tarsal conjunctiva, which has been described in infective or atopic disease, where it may progress to shallowing of the fornix.[7] We looked specifically to see if this was a significant early feature in our CP group with oral or cutaneous scarring. It was found in 28%, but also in 45% of age matched controls, and so is not a specific finding. Moreover, we found that patients with symblepharon lacked this feature, making it unlikely that one precedes the other. Further follow-up of our patients may clarify its significance in CP patients.

Symblepharon itself did appear to be a significant form of scarring, and was found in two (14%) of CP patients who had presented with mouth involvement but were free of ocular symptoms. Our CP group overall thus showed a lower incidence of scarring (43% if fine linear scarring was included) than previous studies of a similar group, presenting to non-ophthalmologists,[4] which had evidence of a cicatrising conjunctival disorder in 67%.

Despite a low incidence of clinical features we found positive IMF in the conjunctiva in 46% of our CP patients. This compares with previous reports of between 20% and 67% conjunctival positivity.[9, 1–4] However, the finding of conjunctival immunoreactants did not correlate with clinical features: one patient who presented acutely showed linear deposition of IgG and C3, as did two patients with symblepharon, but the other three IMF-positive patients lacked any significant symptoms or signs. It has also been suggested that scarring in CP may prevent binding of immunoreactants by destruction of the BMZ antigen involved, but finding positive IMF in clinically uninvolved tissue in both patients who had symblepharon suggests the antigen persists in this site.

In our BP group conjunctival scarring with shrinkage of the lower fornix was found in one patient whose skin features were typical of BP. This has not previously been reported in BP, as it has perhaps been assumed that ocular scarring is a feature only of CP, and the eyes of BP patients may not have been examined in detail. This patient conforms with Wright's description of asymptomatic changes in CP patients.[5] Our finding further suggests confusion in the clinical definition of the two groups with overlap between them.

Immunopathologically our BP group showed a higher rate of positivity than the CP group in all tissues biopsied. The low rate of skin positivity in our BP patients (37%) than in previous reports[2, 20, 21] may reflect the long average duration of disease and clinical mildness in our group at the time of biopsy. Despite this we found in the conjunctiva a surprisingly high rate (73%) of positivity. This compared with 52% positivity from clinically uninvolved lip mucosa in the same patients (Table 3). The results of clinical and IMF comparison in these three sites have been presented in abstract and are to be described in a separate paper.[23, 24] Linear deposition of immunoreactants has been found in the oesophagus and stomach, but not more distally in the gastrointestinal tract in BP,[25] suggesting that the BP antigen is present only in stratified epithelia

The distribution of IMF positivity between the three tissues and the class of immunoreactant found were of interest. Nineteen patients had all three tissues biopsied. In four of these all tissues were negative. In four all tissues were positive, with a similar class of immunoreactant found in all sites It remains to be established whether the tissue immunoglobulins are identical and if they are the same as circulating anti-basement-membrane zone antibodies, which may be found in patients in both groups.[2, 12–15] In six patients uninvolved bulbar conjunctiva was the only source of positive material. The conjunctiva is thus a useful site to examine for diagnostic purposes, particularly in BP, though a definite diagnosis may not be made from this site alone, as 27% are IMF-negative in clinically uninvolved conjunctiva. In CP the rate of positivity is lower, and it may be useful to examine the skin and lip also in patients who present with eye involvement; in two CP patients the conjunctiva was negative for IMF when skin and lip were positive

In all groups of patients and the controls IgA was found in about 75% of biopsies in a non-linear fashion within some of the conjunctival epithelial cells. The significance of this is unknown, but it may represent locally produced IgA adsorbed from tears into the epithelial cells. The appearance has been previously reported.[14] We have looked for secretory piece (the glycopolypeptide which is normally attached to IgA secreted on to mucosal surfaces) in these biopsies (Millard unpublished) with negative results. Further studies into its origin are planned.

We have found bulbar conjunctival biopsy to be simple and well tolerated, though it does ideally require slit-lamp facilities. Most patients found it painless, and there was usually no bleeding. There were no complications apart from a single patient in the CP group who returned with a red painful eye three days after biopsy. She was found to have focal inflammation at the site of biopsy, probably due to too deep a sample, which had included episclera. This rapidly settled with continued topical antibiotic alone Only two patients refused biopsy. Our sample size was adequate for a full set of tests, and did not require specific orientation. Other authors have stressed that biopsy of the fornix from a clinically involved site may be hazardous.[7 26]

Our findings suggest further overlap between CP and BP, as we found significant though often asymptomatic ocular abnormalities in both groups. The 73% positive linear IMF in conjunctiva in BP is an unexpected finding, as it does not correlate with clinical features. This raises further questions about the pathogenicity of immunoreactants within the BMZ. We suggest that biopsy of uninvolved bulbar conjunctiva is an acceptable and valuable technique for diagnosis in the pemphigoid group.

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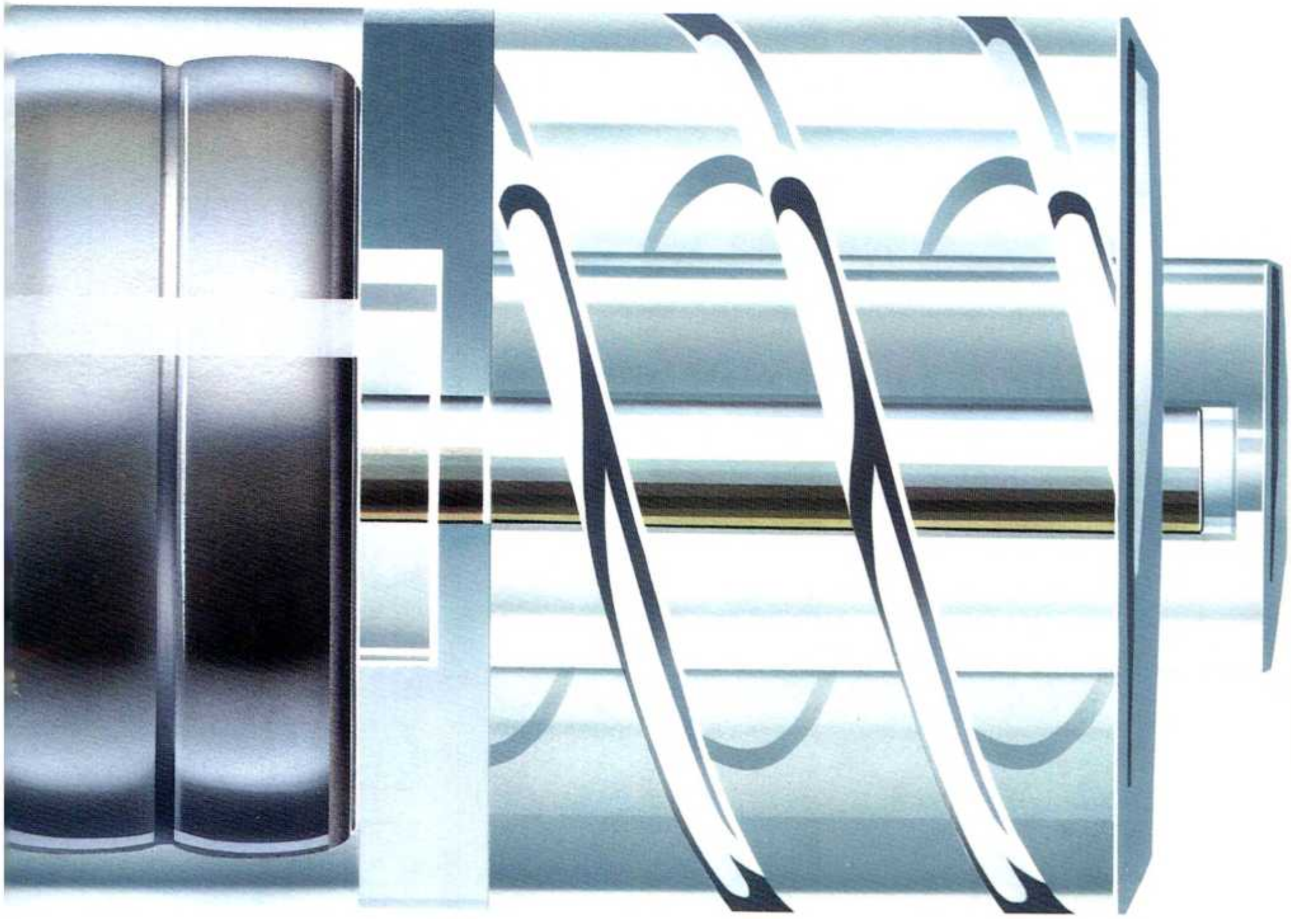

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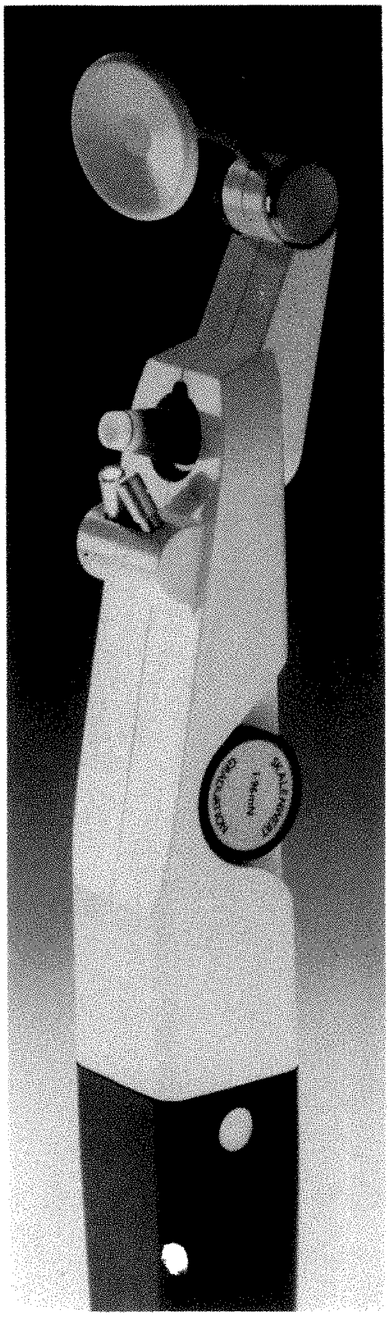

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British Journal of Ophthalmology, 1989, 73, 57–60

Accuracy of routine intraocular lens power calculation in a district general hospital

P T S GREGORY, R M ESBESTER, AND D L BOASE

From Queen Alexandra Hospital, Cosham, Portsmouth

SUMMARY To assess the accuracy of routine preoperative biometry we reviewed all cases of extracapsular cataract extraction with posterior chamber implant performed at Queen Alexandra Hospital in 1985. Of 471 eyes included in the survey 67·9% were within 1·0 D of the expected refraction and 90·7% within 2·0 D. Factors influencing accuracy are discussed. The necessity of routine preoperative biometry is emphasised.

There is increasing evidence of the value of preoperative biometry to calculate the power of an intraocular implant used during cataract surgery to avoid the large range of postoperative refractive error associated with the use of a standard-power lens. This led to the adoption of biometry in our hospital during 1984 and its routine use throughout 1985. The purpose of this study was to measure the accuracy of our biometry and discover reasons for any errors in the hope that these might be minimised in the future.

Materials and methods

All cases of extracapsular cataract extraction with implantation of a posterior chamber intraocular lens (IOL) performed at Queen Alexandra Hospital in 1985 were reviewed, except where penetrating keratoplasty was simultaneously performed. From this total of 528 cases 57 cases were excluded for various reasons (Table 1), leaving 471 eyes in the survey.

A Haag-Streit Javal-Schiøtz keratometer was used for keratometry in every case. Axial length was measured with a Coopervision Ultrascan 2, 10 MHz, liquid probe until September 1985, when a 3-M Digiecho, 10 MHz, solid probe was used mounted on a double table with the keratometer. This arrangement made biometry much more rapid and convenient. We used IOLAB Sinskey style lenses with 10° forward angled loops, many with laseridge and ultraviolet filter (Model nos. G707G and G757G). Biometry was carried out by optometrists, consultants, and junior doctors. Twelve people with varying degrees of experience made the measurements.

For each patient the following steps were taken. First, keratometry and axial length measurement of each eye were performed and spectacle prescription recorded. A decision was then made on the desired postoperative refraction. Generally we aimed for emmetropia or slight myopia, but in an ametrope with vision of 6/24 or better in the other eye we aimed for two dioptres less ametropia than in the other eye to avoid possible problems from aniseikonia and anisometropia.

Next the power of intraocular lens for emmetropia was calculated from the Sanders, Retzlaff, and Kraff (SRK) formula[1]:

$$\underset{\text{(dioptres)}}{\text{IOL power}} = \text{A} - 2{\cdot}5 \underset{\text{(mm)}}{\text{(axial length)}} - 0{\cdot}9 \underset{\text{(dioptres)}}{\text{(mean keratometry)}}.$$

The A constant recommended for this lens is 116·8, but may be modified by any surgeon in the light of his experience.

Where ametropia was desired, this calculation was adjusted by the formula:

$\text{Power}_{\text{am}} = \text{Power}_{\text{emm}} \pm \frac{3}{2}$ (dioptres ametropia required). (The effectivity of a lens at the implant plane is ⅔ that of a lens at the spectacle plane.)

For example, if the SRK formula suggested a 21-dioptre lens for emmetropia in a given case, then if 2 dioptres myopia were desired postoperatively a 24-dioptre lens would be required.

We now decided on the power of implant to use, bearing in mind the desired postoperative refraction and also that lenses were available only in half-

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Table 1 *Patients excluded from survey*

1. Biometry not performed:	24 cases
(*a*) No reason given: 14 cases	
(*b*) Reasons given: 10 cases: 6 difficult eyes	
4 difficult patients	
2. Post-op. refraction data unavailable:	27 cases
(*a*) 9 Cases where refraction was not accurately recorded because acuity was too low to confirm retinoscopy subjectively:	
2 central retinal vein occlusions	
2 disciform macular degenerations	
1 ischaemic optic neuropathy	
1 retinal detachment	
1 cystoid macular oedema	
1 open-angle glaucoma	
1 implant subluxation	
(*b*) 6 Cases died before refraction.	
(*c*) 5 Cases were refracted elsewhere.	
(*d*) 3 Cases moved away before refraction.	
(*e*) 3 Cases acuity 'too good' for refraction.	
(*f*) 1 Case did not attend for follow-up.	
3. Records missing despite repeated searches:	5 cases
4. Biometry data illegible:	1 case
Total exclusions	57 cases

dioptre steps. We calculated the exact postoperative refraction expected from this approximately correct intraocular lens. For example: Suppose biometry indicates that a 20·85 D implant will give emmetropia. A 21·0 D implant is used. Postoperatively this eye should have a refraction of: $2/3\,(20{\cdot}85-21{\cdot}0)=-0{\cdot}10$ D. This is the expected refraction with which the actual postoperative refraction is compared to assess the acuracy of our biometry.

Six to eight weeks after operation the eye was refracted and astigmatism with the rule was corrected by cutting and removing some or all of the interrupted 10-0 nylon sutures[2] (see below).

The final refraction was performed within 12 weeks, and the difference between this and the expected refraction was recorded in each case. These figures quantify the accuracy of our biometry. As a comparison, an estimate was also made (by means of the two-thirds effectivity factor) of the expected postoperative refraction if a 21·0-dioptre lens had been used in each case.

Results

The accuracy of our biometry was determined by recording the dioptric value of: (actual refraction) − (expected refraction) in each case.

Over all cases the mean of this difference was −0·17 dioptre, indicating that on average the eyes ended up 0·17 dioptre more myopic than expected. The standard deviation of this difference was 1·71 dioptres.

The equivalent figures estimated if a 21·0 D lens had been used in each case were: mean postoperative refraction −1·08 D, with standard deviation 2·68 D. An average of emmetropia for our patients would therefore have been achieved if the standard lens power had been 19·38 D $(21+3/2\,(-1{\cdot}08)=19{\cdot}38)$. The large standard deviation would of course not be affected.

The only caution in comparing these figures is that our accuracy is not totally transferred to the patient owing to the half-dioptre steps between available implants. From this a patient can expect on average 0·083 D less accuracy than if an infinite range of powers were available. This is evidently of no practical consequence.

The percentage of cases falling in given dioptre

Table 2 *Percentage of cases within dioptre ranges*

Biometry
90·66% of cases were within ±2·0 D of the expected refraction.
84·29% of cases were within ±1·5 D of the expected refraction.
67·94% of cases were within ±1·0 D of the expected refraction.
40·76% of cases were within ±0·5 D of the expected refraction.
Standard 21·0 D lens
70·02% of cases were within ±2·0 D of emmetropia.
56·96% of cases were within ±1·5 D of emmetropia.
42·83% of cases were within ±1·0 D of emmetropia.
20·56% of cases were within ±0·5 D of emmetropia.

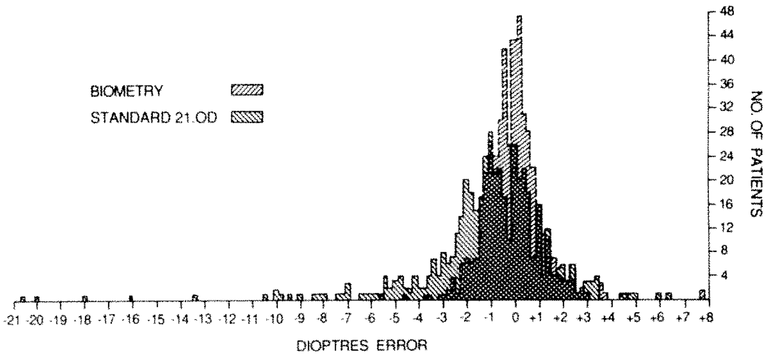

Fig. 1 *Numbers of patients in 0·2 dioptre steps.*

ranges from biometry and the standard 21·0 D lens is shown in Table 2, and a histogram of numbers of eyes in 0·2 dioptre steps is shown in Fig. 1

As mentioned above, in some cases sutures were cut to reduce astigmatism. This was generally done when there was a positive cylinder of 2 or more dioptres with a near vertical axis (60°–120° approximately) In all, 384 sutures were removed from 100 eyes, with a mean reduction of 1·21 dioptres cylinder per suture. Overall mean sphere refraction of an eye was not affected by suture removal.

Discussion

Other surveys[1 3–17] have studied the value of preoperative biometry for calculating the power of intraocular lenses for the correction of aphakia. This survey is unusual in examining a large number of cases and representing a whole year's workload from a district general hospital. Our figures compare favourably with other published studies.[4–7 10–13 18] We were anxious to include all possible cases regardless of biometric difficulty. A subjective confirmation of refraction was obtained in most cases, but in some cases retinoscopy was considered sufficiently accurate.

Our figures of 90·66% of cases within ±2·0 dioptres of expected refraction show that encouraging accuracy is being achieved. In some centres biometry is not undertaken and a standard power lens is used (usually 21·0 D for the type of posterior chamber lens we are using). Our figures show that this method would have produced a much wider range of postoperative refraction than did biometry.

Other centres vary the implant power according to the pre-cataract spectacle refraction. The usual formula used is:

$$\text{IOL power}=21+3/2\ (\text{pre-cataract spectacle refraction}).$$

It is well established that the dioptric power of an eye depends on corneal curvature, crystalline lens position and power,[3 19] and axial length. In any group of emmetropic eyes there will be found a wide range of these four variables, despite their identical overall refraction. This is why spectacle refraction alone gives such a poor guide to implant power, as has been shown by other studies.[3–5 8 19] There is also little correlation between fellow eyes of axial length, keratometry, and anterior chamber depth.[19]

We re-examined the records of our worst results—that is, the 44 eyes where the final refraction differed from expected by 2·0 dioptres or more The errors ranged from −20·0 dioptres (subsequently remeasured and found to have been grossly mismeasured preoperatively) to +8·75 dioptres. We listed the apparent main causes of error (see Table 3).

Table 3 *Reasons for inaccuracy*

	No.	%
No obvious reason	16	36·4
Biometric difficulties	15	34·0
Long eyes	13	29·5
Short eyes	1	2·3
Proved mismeasurement	5	11·4
Surgical problems	3	6·8
Records unavailable	1	2·3

In some cases two or more of these factors were present.

Biometric difficulties were ascribed to a number of factors: (*a*) Mental and physical problems made measurements technically difficult. (*b*) Ocular problems were: dense cataracts causing poor transmission of ultrasound; cataracts and macular disease causing poor fixation; corneal irregularities causing poor keratometry. (*c*) Many of these cases were measured by inexperienced biometricians.

Several cases showing the more extreme errors were remeasured and found to have been wrongly measured before surgery. We found only one short (<21 mm) eye in the inaccurate group, but 10 long eyes (>25 mm). This is 22·7% of our worst cases in comparison with 7% of the whole survey. Some authors advocate the use of a different formula to calculate implant power in long and short eyes.[11 14 20]

Surgical problems may have contributed to the inaccuracy of the results of biometry in three of these cases. In one case the implant was nasally displaced, potentially affecting the refraction; one wound had to be resutured; and one posterior capsule was ruptured.

Another possible source of error is the degree of accuracy of the stated implant power, which has been questioned, but which recent studies have shown to be of a very high standard.[21 22] We have therefore relied on the quality control figures of the manufacturers.

Our results show that preoperative biometry is a practicable routine procedure in a district general hospital and has proved very useful in the accurate correction of aphakia with intraocular lens implantation. Our results compare well with those in other published series despite the fact that measurements were undertaken by no fewer than 12 people and all difficult cases have been included wherever possible. We consider that biometry should be part of the routine preoperative examination in all cases where intraocular lens implantation is being considered.

We thank the Consultants at Queen Alexandra Hospital for permission to report on their patients, and Lieut. Commander J R Wills, RN, for help with data analysis

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Rabies: ocular pathology

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SUMMARY Ocular pathology in the first European case of human bat-borne rabies is described. The patient was a 30-year-old bat scientist who seven weeks after bat bite developed neurological symptoms and died 23 days later. Rabies virus antigens were detected in brain smears. After extensive virological studies the virus turned out to be a rabies-related virus, closely resembling the Duvenhage virus isolated from bats in South Africa in 1980. By light microscopy focal chronic inflammatory infiltration of the ciliary body and of the choroid was found. PAS-positive exudate was seen in the subretinal and in the outer plexiform layers of the retina, and retinal veins showed endothelial damage and perivascular inflammation. Many of the retinal ganglion cells were destroyed. The presence of rabies-related viral antigen in the retinal ganglion cells was shown by positive cytoplasmic immunofluorescence, though electron microscopy failed to identify definite viral structures in the retina. By immunohistochemistry glial fibrillary acidic protein was observed in the Müller's cells, which are normally negative for this antigen but express it as a reactive change when the retina is damaged. Synaptophysin, a constituent of presynaptic vesicles of normal retinal neurons, was not detected in the retina.

Rabies, a neurotropic rhabdovirus infection of worldwide occurrence, is usually transmitted to humans by animals, most often by dog or cat bite.[1] In addition to transmission via animal bites the virus can penetrate through intact mucous membranes or abraded skin from the saliva of a rabid animal. There are also cases of airborne transmission.[2 3] However, the only reported cases of human-to-human transmission have occurred via corneal transplants,[4-10] and rabies virus has been experimentally shown to spread to cornea by axonal transport.[11 12] In view of this it is surprising that, to the best of our knowledge, there are no reports of ocular pathology in human rabies.

Though human rabies caused by bat bite has long been recognised on the American continent[1] it has only recently become evident that even insectivorous European bats are carriers of rabies-related viruses,[13 14] constituting a potential hazard to humans.

The purpose of the present paper is to describe the ocular pathology in the first European case of human bat-borne rabies.[15 16]

Case report

The patient was a 30-year-old man who had previously been in excellent health. He was a zoologist who had been studying bats in different parts of the world but had never been vaccinated against rabies. Four and a half years before his illness he had been bitten by a bat in Malaysia and one year before in Switzerland. Fifty one days before the onset of his neurological symptoms he had been caring for a bat (*Myotis daubentoni*) at his home. The bat had behaved oddly and had bitten him several times. After apparent improvement of the bat the patient had let it go and it was never examined virologically

Seven weeks later the patient felt numbness and pain in his right arm and neck and developed an ascending paralysis of the Guillain-Barré type. He was admitted to the Helsinki University Central Hospital, where he developed hyperexcitability, hyperventilation, and spasms. Rabies was suspected and the patient was treated intensively on this hypothesis, though virological investigations during life could not confirm the diagnosis. The patient died 23 days after the onset of the first neurological symptoms.

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Post-mortem neuropathological and virological studies showed severe encephalitis and peripheral neuritis. Rabies virus antigens were detected in brain smears. After inoculation of brain material into newborn and 3-week-old mice the virus was further characterised by electron microscopy and a set of monoclonal antibodies (Roine *et al.* and Haltia *et al.*, in preparation). It turned out to be closely related to the Duvenhage virus isolated from bats in South Africa in 1980. It was antigenically similar but not identical with the rabies related viruses recently isolated from bats in Germany, Poland, and Denmark.[14]

Materials and methods

The eyes were fixed two hours after death in 4% phosphate buffered formaldehyde solution. After fixation they were cut in the horizontal plane and embedded in paraffin. Small selected specimens were postfixed in 2% phosphate-buffered glutaraldehyde and routinely processed for transmission electron microscopy. Paraffin sections were stained with haematoxylin-eosin, van Gieson, and periodic acid-Schiff (PAS) methods. The direct immunofluorescence method was used to detect the presence of rabies antigen in the ocular tissues, by means of a commercial antirabies immune globulin labelled with fluorescein isothiocyanate, isomer I (BBL Microbiology Systems, Cockeysville, MD, USA).

The immunohistochemical stainings to demonstrate neuron-associated and glia-associated antigens in formalin-fixed and paraffin-embedded tissues were carried out with a commercial version (Vectastain ABC Kits for Rabbit and Mouse IgG, Vector Laboratories, Burlingame, CA, USA) of the avidin-biotinylated peroxidase method[17] as previously described in detail.[18–20] The primary antibodies used were antineuron specific enolase (Code A589, Lot 084, dilution 1:500) and anti-S-100-protein antisera (Code Z311, Lot 113, dilution 1:100) from Dakopatts a/s (Glostrup, Denmark), monoclonal antisynaptophysin antibodies (Code 902322, Lot 10644526-01, dilution 1:5) from Boehringer-Mannheim Biochemica (Mannheim, FRG), as well as monoclonal antiglial fibrillary acidic protein[21] and anti-200 kD neurofilament triplet protein antibodies (NFI[21], both diluted 1:50) generously provided by Dr Ismo Virtanen (Department of Pathology, University of Helsinki). Prior to immunohistochemical staining the sections were pretreated with 0·4% pepsin (E Merck, Darmstadt, FRG) in 0·01 N hydrochloric acid for 15 min at 37°C to reduce background and to enhance the intensity of specific staining. Five formalin-fixed and paraffin-embedded human eyes obtained from necropsies at the Department of Forensic Medicine,

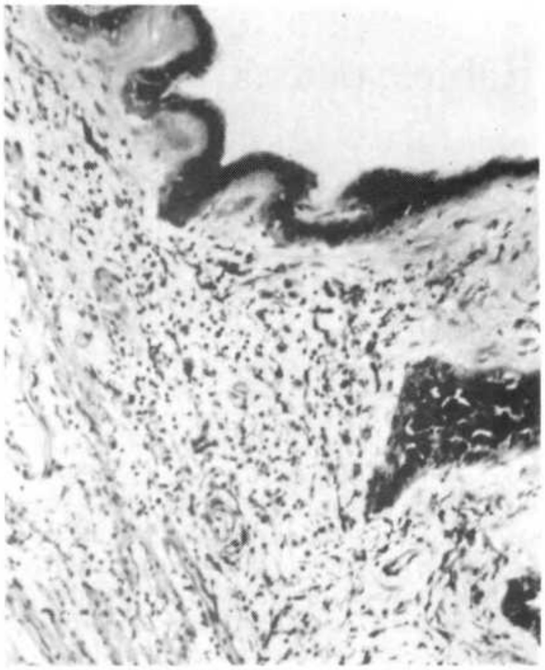

Fig. 1 *Chronic mononuclear inflammatory cell infiltration in the ciliary body. PAS, ×100.*

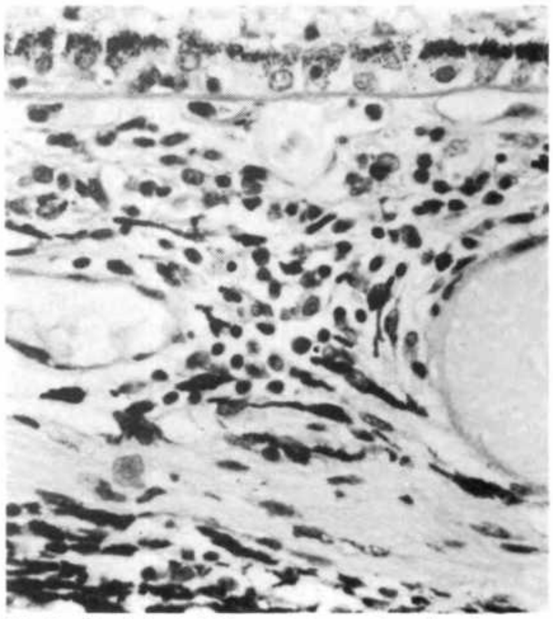

Fig. 2 *Focal chorioiditis consisting mainly of lymphocytes and plasma cells. Slight depigmentation of the retinal pigment epithelial cells. PAS, ×440.*

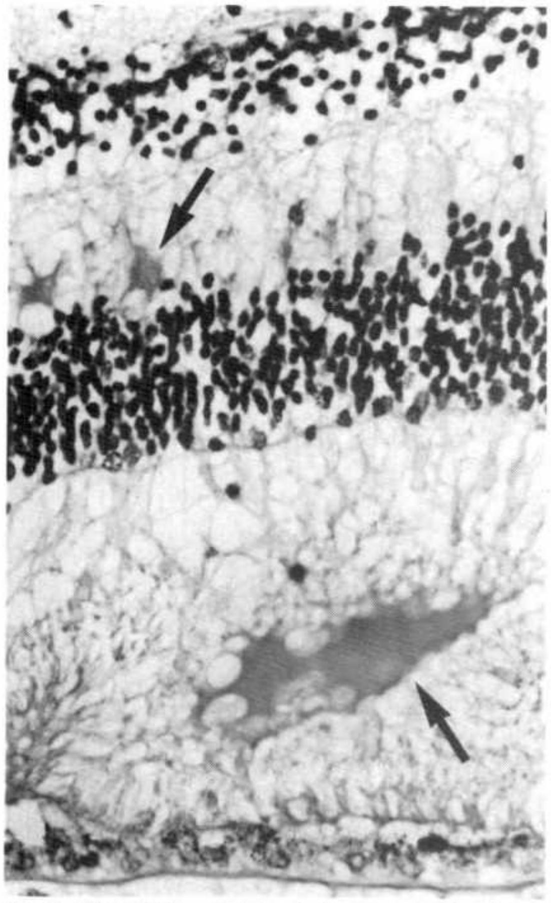

Fig. 3 *PAS-positive exudation in the outer plexiform layer and subretinal space (arrows). PAS, ×475.*

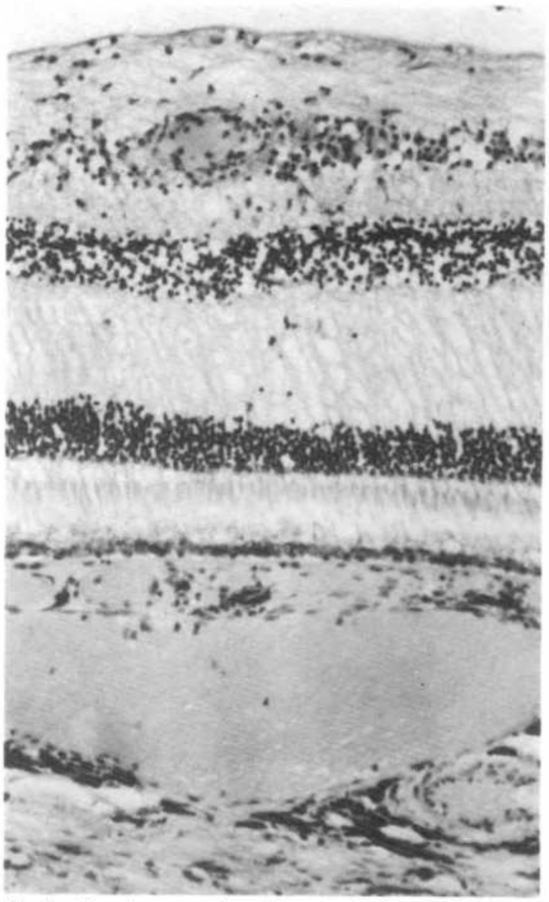

Fig. 4 *Good preservation of the visual cells as well as only a slight inflammatory involvement of the choroid are seen. In the nerve fibre layer perivascular inflammatory infiltration is present. PAS, ×108.*

University of Helsinki, and previously referred to the Ophthalmic Pathology Laboratory, were used as control post-mortem material. Except for autolytic changes observed in photoreceptor cells and cystic degeneration of the ora serrata region in some specimens, these eyes were entirely normal under the light microscope.

Results

MORPHOLOGICAL FINDINGS

Macroscopic findings were within normal limits. By light microscopy a chronic inflammatory reaction consisting of lymphocytes and plasma cells was seen in the ciliary body and as foci in the choroid (Figs. 1, 2). The pigment epithelium of the retina showed some loss of pigment especially in the posterior fundus (Fig. 2). The overall structure of the sensory retina, including the visual cells, was rather well preserved. PAS-positive exudate was seen as foci in the subretinal layers as well as in the outer plexiform layer (Fig. 3). In the retinal nerve fibre layer perivascular inflammatory foci consisting of lymphocytes and plasma cells were seen. The endothelium of the retinal veins was destroyed and the lumen almost totally occluded in places (Figs. 4, 5). In semithin sections many of the ganglion cells were seen to be destroyed and the nuclei of many bipolar cells were altered (Fig. 6). As evidence of absence of post-mortem autolysis good preservation of the retinal visual cells can be seen. Electron microscopic studies failed to reveal structures positively identifiable as viral elements.

IMMUNOHISTOCHEMICAL FINDINGS

Sections stained by the rabies antibody showed small

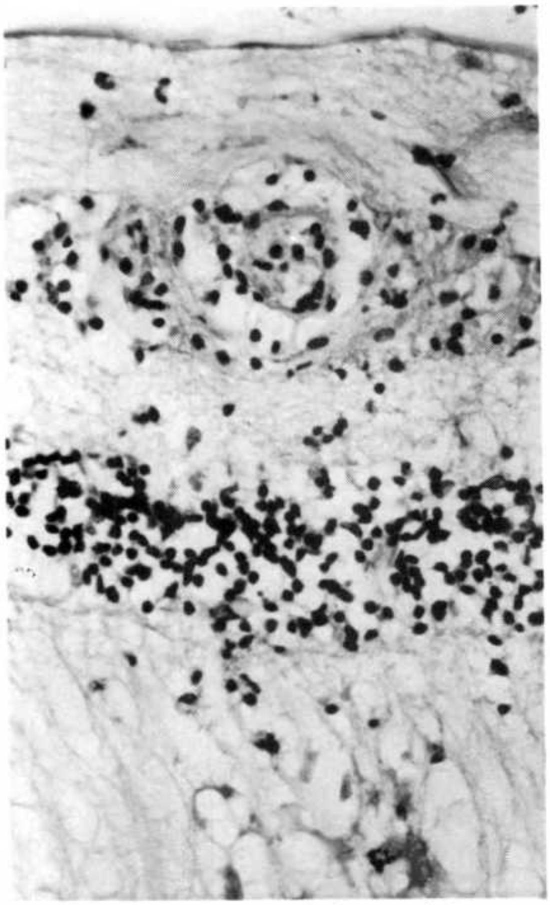

Fig. 5 *Vasculitis and perivasculitis have resulted in an almost complete obstruction of the retinal vessel lumen. Exudate in the outer plexiform layer. PAS, ×477.*

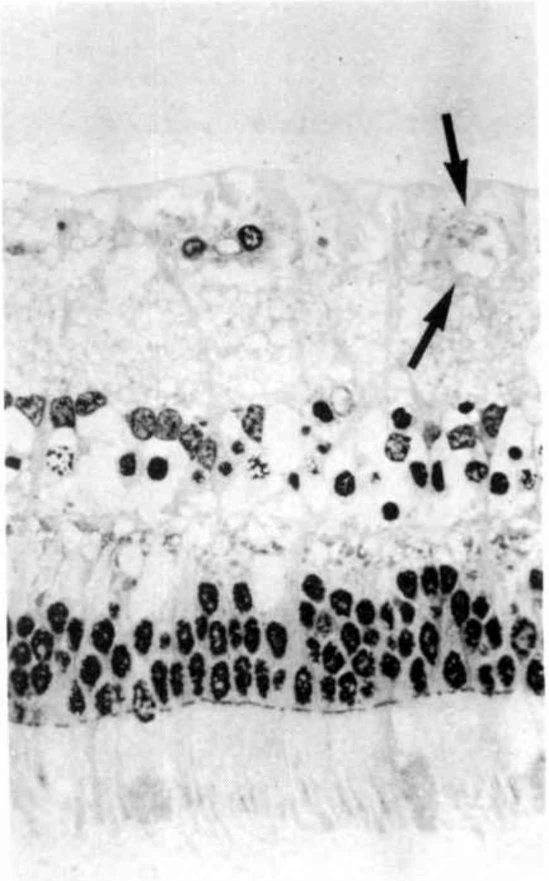

Fig. 6 *Semithin section of the retina. Remnants of a destroyed ganglion cell (arrows) and partial disappearance of the bipolar cells are seen while nuclei of the glial cells have been preserved. The rod and cone nuclei show altered chromatin structure. Toluidine blue, ×477.*

green intensely fluorescing granules in the cytoplasm of many of the remaining retinal ganglion cells (Fig. 7) (as well as in the patient's brain and in a rabies-infected mouse brain) but not in non-infected control tissues.

In human necropsy eyes of normal appearance on light microscopy the monoclonal antibody to glial fibrillary acidic protein (GFAP) reacted with astrocytes in the nerve fibre and ganglion cell layers (Fig. 8A), as well as with a few Müller's cells close to the ora serrata. In the central retina all Müller's fibres were negative for GFAP. However, in the eye from the rabies patient, Müller's cells expressed GFAP throughout the retina (Fig. 8B). The antiserum to S-100 protein, another marker for retinal glia, labelled retinal astrocytes and a few Müller's cells in all specimens studied.

The polyclonal antiserum to neuron-specific enolase reacted strongly with photoreceptor cells, but labelled the inner nuclear, inner plexiform, and nerve fibre layers only weakly. A positive reaction was also seen in the remaining ganglion cells. The 200 kD neurofilament triplet protein was detected in neuronal processes of the nerve fibre layer and optic nerve, as well as in occasional nerve fibres in the inner plexiform layer. While these neuronal markers were identically expressed in all retinas examined, both plexiform layers reacted positively for synaptophysin in the control eyes (Fig. 8C), but no reactivity was detected in the eye from the rabies patient (Fig. 8D).

Discussion

Several viruses are known to cause intraocular

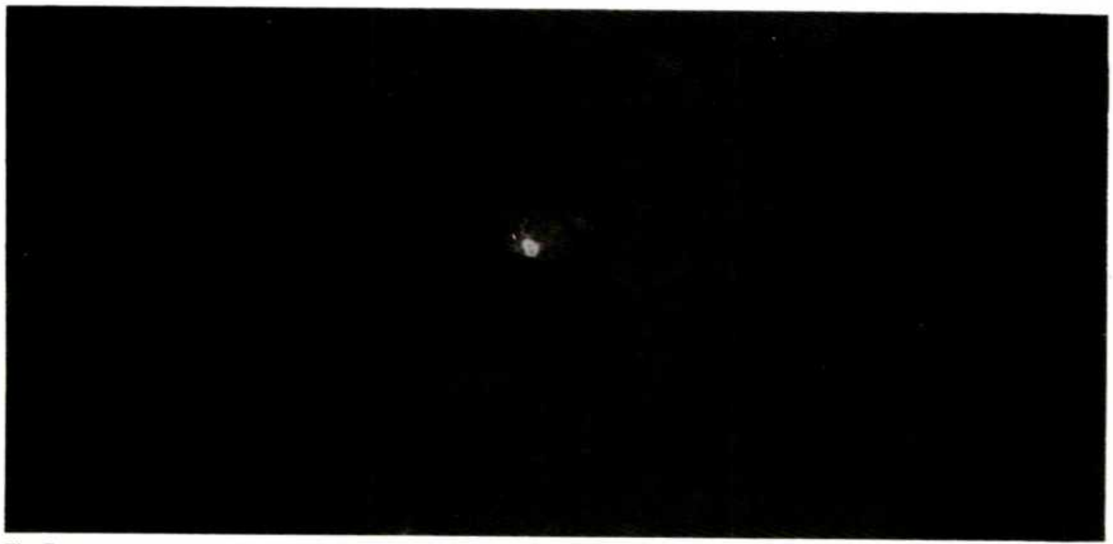

Fig. 7 *A remaining ganglion cell shows a strongly fluorescent cytoplasmic inclusion body after staining with rabies antibody. Direct immunofluorescence method, ×660.*

lesions. Herpes simplex virus (type 1) is probably the most common cause of viral intraocular inflammation. Uveitis associated with keratitis is characterised by a non-granulomatous inflammatory infiltrate composed of lymphocytes and plasma cells.[22] Necrotising retinitis in adults occurs only with immunodeficiency.[23] Varicella zoster may induce intraocular changes when the nasociliary branch of the trigeminal nerve is involved. When choroiditis is present, it is focal and of the granulomatous type, usually without necrosis.[24] In terms of the nature of the uveal inflammatory lesion this type of uveitis is very different from that found in the present case. In cytomegalic inclusion disease a focal progressive

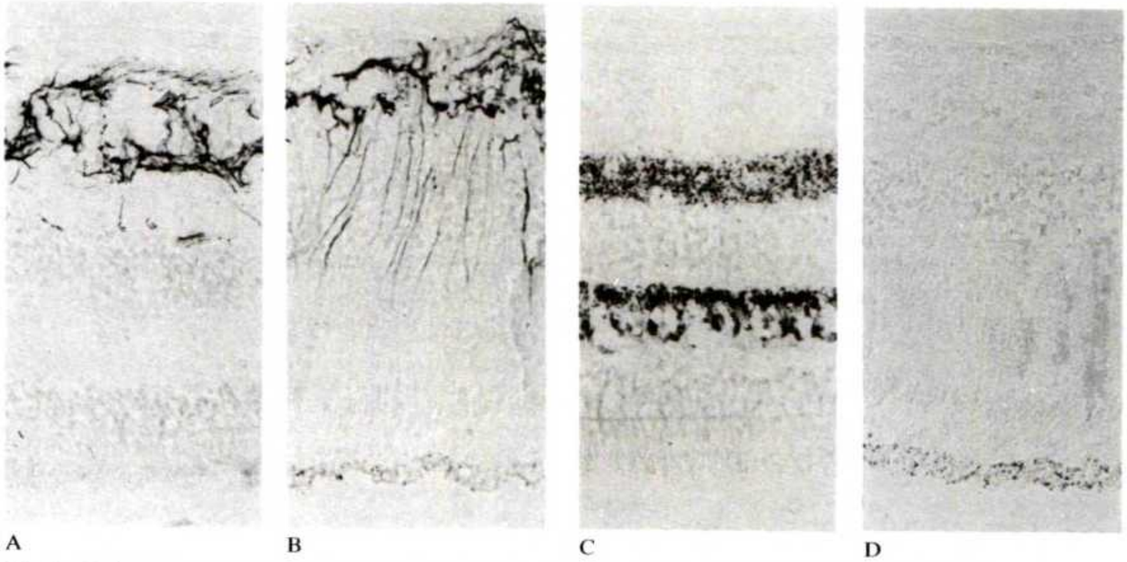

Fig. 8 *Differences in antigenic properties of human retina from the rabies patient and from a control necropsy eye (immunoperoxidase staining, ×210).* A. *In the necropsy eye only astrocytes express glial fibrillary acidic protein (GFAP).* B. *In the rabies eye an additional positive reaction is observed in slender Müller's fibres reaching towards the outer limiting membrane.* C. *In the necropsy retina both plexiform layers express synaptophysin.* D. *The entire rabies infected retina is negative for synaptophysin.*

necrotising inflammation is strikingly confined to the retina. It has been repeatedly shown that the vitreous and the choroid are usually spared from any inflammatory changes even in the areas of severe retinal necrosis.[25,26] Retinal necrosis is also the main ocular feature of measles retinopathy.[27] These findings bear no reflections to the present case, with focal non-granulomatous cyclitis and choroiditis as well as involvement mainly of the inner retina.

To our knowledge no descriptions of ocular pathology in human rabies are available. After inoculation against rabies, neuroretinitis has been described[28] as well as bilateral optic neuritis and retinal haemorrhages.[29] Rabbits inoculated with rabies virus by Dejean showed extraocular muscle palsy, disappearance of the corneal sensitivity, corneal clouding, venous congestion of the retina and of the optic nerve as well as clouding of the vitreous. At histopathological study Negri-like bodies could be identified in the retinal ganglion cells.[30] Arguello and Melita[31] described two cases, a boy bitten on the right side of his face with facial paralysis of the same side and mydriasis, and an adult showing conjunctival congestion and retinal haemorrhages In their 100 rabbits inoculated with rabies virus choroidal haemorrhages were found. In comparison with the rabbit study of Dejean[30] our findings agree only with regard to the involvement of the retinal ganglion cells. No changes in the vitreous or in the cornea could be identified Our immunofluorescence studies showed the presence of rabies virus antigen in the cytoplasm of many of the remaining retinal ganglion cells in the form of small intensely fluorescing granules. They apparently correspond to the Negri-like bodies found by Dejean[30] in rabies infected rabbits and indicate that the retinal lesions are directly induced by the virus.

Two further immunohistochemical deviations from the usual pattern seen in human necropsy eyes appearing normal on light microscopy were evident. Glial fibrillary acidic protein (GFAP) was observed in Müller's cells, which are normally negative for this antigen.[32–34] In the control necropsy eyes only a few GFAP-positive Müller's cells were seen at the ora serrata, confirming previous reports.[34,35] It appears that Müller's cells in the rabies eye have accumulated GFAP in response to the retinitis and retinal vasculitis observed. Previous observations have shown that GFAP is a relatively sensitive indicator of damage to retina that results from mechanical trauma,[35] photoreceptor degeneration,[36,37] intra-ocular tumours,[19] glaucoma, retinal detachment, or inflammatory reaction involving the vitreous cavity.[32]

On the other hand synaptophysin, a constituent of presynaptic vesicle membranes that is normally present in synapses of both plexiform layers of the mammalian retina,[38] was absent in the rabies eye. This was unexpected, since synaptophysin was detected in all control necropsy eyes, obtained after comparable delays after death, albeit less strongly than we have seen in surgical specimens. There is a possibility that the amount of synaptophysin in retinal neurons was diminished before death, though this remains conjectural at present. There was no obvious change in the expression of other neuronal markers examined. The inner retinal layers, however, reacted more weakly with antiserum to neuron-specific enolase than is seen in surgical specimens.[18] This may reflect virus-induced degeneration and loss of the retinal ganglion cells and bipolar cells in addition to post-mortem change.

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Congenital adduction palsy and synergistic divergence: a clinical and electro-oculographic study

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SUMMARY We studied two patients with a peculiar congenital disturbance of ocular motility in which the horizontal movements of the left eye were always opposite the normal expected direction. The common features were: (1) congenital monocular adduction palsy and exotropia of the left eye; (2) simultaneous abduction of both eyes (divergence) on attempted dextroversion; (3) ocular torticollis, head turned to the right; and (4) inverse nystagmus of the left eye, occurring spontaneously as well as during optokinetic and vestibular testing. Clinical and electro-oculographic findings suggested a close relationship to Duane's retraction syndrome and supported the concept that innervational mechanisms were responsible for the phenomenon.

Congenital unilateral paralysis of adduction associated with simultaneous bilateral abduction on attempted gaze into the field of action of the paretic medial rectus muscle is a rare entity. We have been able to find nine reported cases.[1–7] Although the major defect is a congenital failure of adduction, the most striking clinical finding is that on attempted adduction the affected eye moves further into abduction and thus causes extreme divergence.

In this communication we briefly review the features of the reported cases and analyse the clinical and electro-oculographic findings in two personally examined cases.

Case reports

CASE 1

A 3-year-old girl was referred to the Institute of Ophthalmology because of congenital adduction paralysis and variable exotropia of the left eye associated with torticollis to the right. Neurological examination at the age of 8 months revealed no significant abnormalities except for borderline skull measurements.

We examined the child in 1981. The visual acuity was RE 20/25 and LE 20/80. Cycloplegic refraction was +3·5 D in both eyes. There was a permanent head turn to the right; this kept the eyes straight (Fig. 1A). With forced straightening of the head, the right eye abducted beyond the midline while the left eye remained exotropic (Fig. 1B). Attempted dextroversion resulted in first, extreme exotropia due to divergence of both eyes (Fig. 1C); secondly, simultaneous abduction nystagmus in both eyes with the fast phase beating temporally; and, thirdly, narrowing of the left palpebral fissure. On levoversion the right eye adducted normally and the extropia of the left eye decreased, so that the eyes became parallel (Fig. 1D). Adduction of the left eye beyond the midline could not be provoked by the oculocephalic manoeuvre or optokinetic stimulation.

No pupillary reactions accompanied any of these ocular movements. Under general anaesthesia the forced ductions confirmed the increased resistance to adduction of the left eye. Abduction of the left eye and the forced ductions of the right eye were normal. Audiometry, *x*-ray films of the skull and cervical spine, and cerebral computed tomography were normal

CASE 2

A 23-year-old male with multiple congenital abnormalities described as arthrogryposis multiplex congenita was referred to the Institute of Ophthalmology in 1983 because of congenital exotropia and

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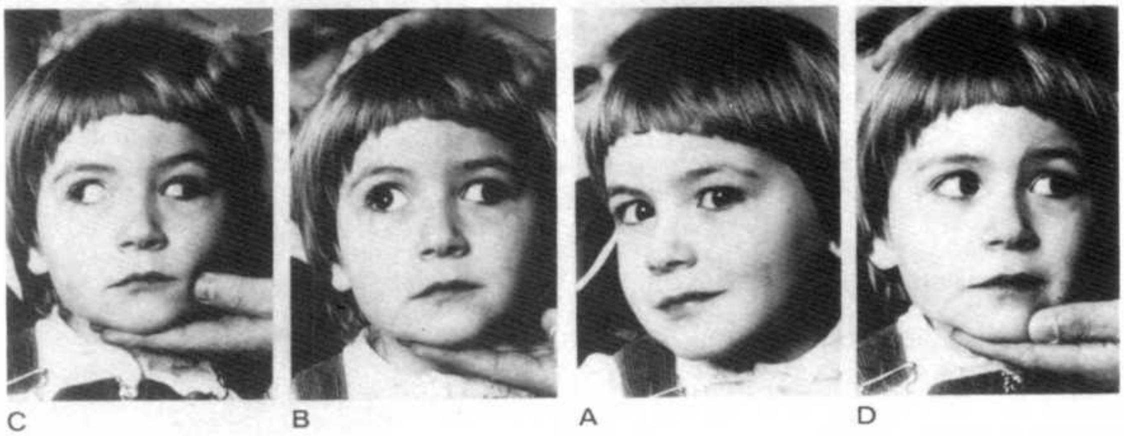

Fig. 1 *Case 1.* A: *Looking forward with permanent head turn to the right.* B: *Exotropia on forced straightening of the head.* C: *Extreme exotropia on attempted gaze to the right. Note that the left eye moves further into abduction, and there is narrowing of the left palpebral fissure.* D: *Decreased exotropia of the left eye on gaze to the left. Note that the exoptropia of the left eye is maximal on gaze to the right and minimal on gaze to the left.*

adduction paralysis of the left eye. At previous strabismus surgery, under general anaesthesia, he was found to have a short and tight left lateral rectus muscle and a thin and atrophic left medial rectus muscle. Following maximal recession of the left lateral rectus muscle and 10 mm resection of the left medial rectus muscle the eyes were parallel for a short time, while the adduction palsy persisted.

The visual acuity was 20/20 in the right eye and 20/200 in the left eye. Cycloplegic refraction was RE +1·0 D, and LE +1.25 D. Slit-lamp examination and funduscopy were normal in both eyes. There was a head turn to the right (Fig. 2A). In the primary position there was a left exotropia of 40° and hypotropia of 15° with absent adduction of the left eye (Fig. 2B). On attempted dextroversion both eyes

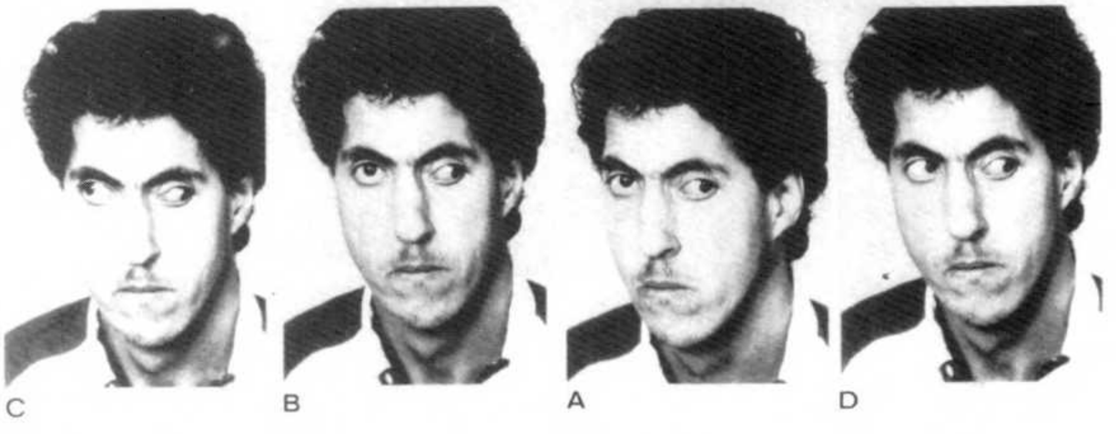

Fig. 2 *Case 2.* A: *Looking forward with permanent head turn to the right, exotropia and hypotropia of the left eye.* B: *Increasing exotropia on forced straightening of the head.* C: *Extreme exotropia on attempted gaze to the right. Note that the left eye moves further into abduction, and there is narrowing of the left palpebral fissure.* D: *Decreased exotropia of the left eye on gaze to the left. Note that the exotropic position of the left eye is maximal on gaze to the right and minimal on gaze to the left.*

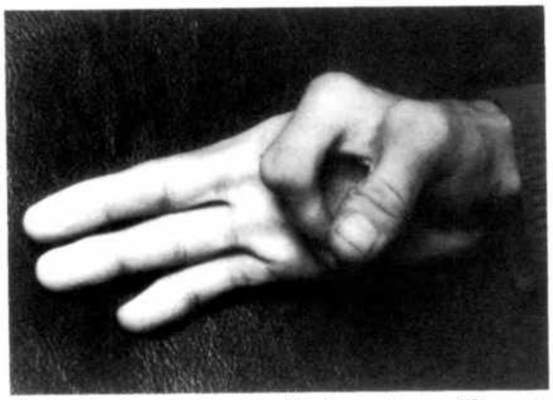

Fig. 3 *Flexion contractures of the first and second fingers in patient 2.*

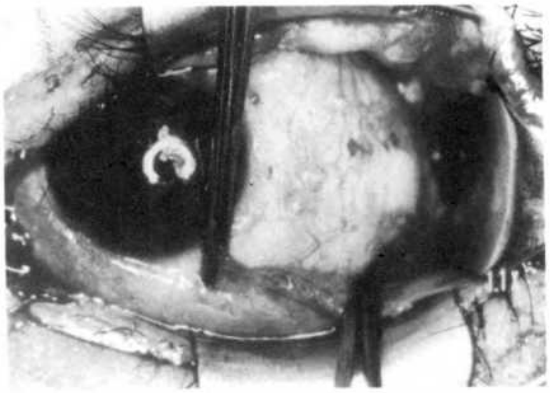

Fig. 4 *Absence of left lateral rectus muscle insertion, as a result of previous strabismus surgery, demonstrated during the second surgical procedure in patient 2.*

abducted and became extremely divergent (Fig. 2C); this was associated with retraction of the left globe and narrowing of the palperbral fissure. On levoversion the right eye adducted normally and the exotropia of the left eye decreased (Fig. 2D). The amounts of exotropia and hypotropia of the left eye were clearly less in levoversion (Fig. 2D) than in dextroversion (Fig. 2C). There was underaction of the depressor and levator muscles of the left eye.

General examination disclosed flexion contractures of the first and second fingers of both hands (Fig. 3), a short atrophic club-footed right leg, and a deformed left foot. The face was narrow and the palate high. Otolaryngological examination disclosed deformation of the external ears. Audiometry was normal. *X*-ray films of the cervical spine and skull and cerebral CT scans were all normal. There were no cardiopulmonary abnormalities and the intelligence was normal.

Because of the severe exotropia and the ugly head posture the patient requested another surgical intervention. A large loop recession of the left lateral rectus and resection of the left medial rectus were planned. Under general anaesthesia forced duction testing of the left eye showed moderate restriction of adduction; forced ductions of the right eye were

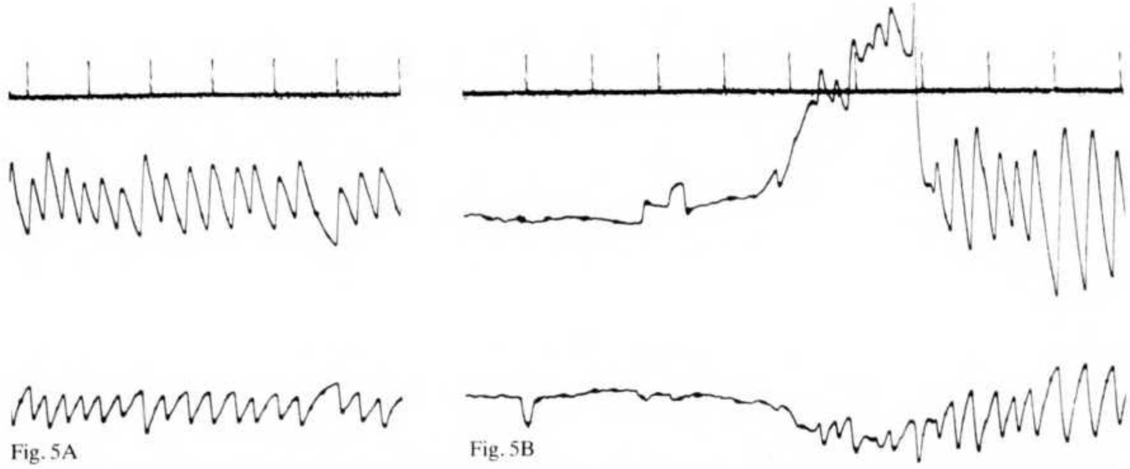

Fig. 5A

Fig. 5B

Fig. 5 *Electro-oculographic recordings in case 1. Tracings from top to bottom in Figs. 5, 6, 7A, 8 time (seconds), right and left eye position. Upward deflection signals eye movement to the right; downward deflection signals eye movement to the left. Position calibration was not feasible in the case. Note that the movement of the left eye is always opposite to the movement of the right eye, and that the divergent-convergent nystagmus in the primary position (*A*) is enhanced by gaze to the right (right half of panel* B*) and disappears on gaze to the left (left half of panel* B*).*

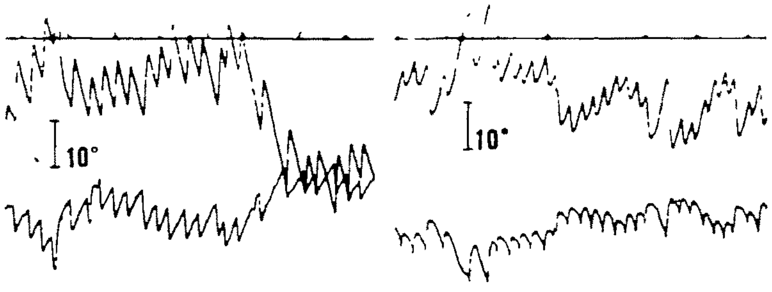

Fig 6A (left) Fig. 6A (right)

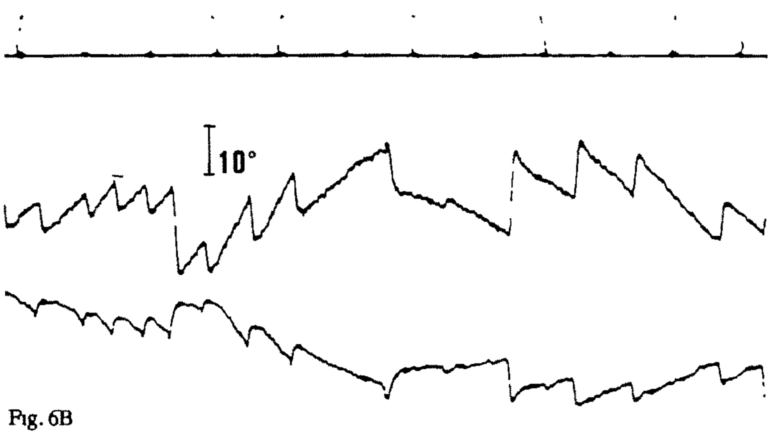

Fig. 6B

Fig. 6 *Responses to evoked nystagmus in case 2. right eye gives normal responses, left eye gives abnormal (opposite) responses.* A: *Optokinetic stimulation; black-and-white stripes, each of 7·5° width, moving at 40° per second, to the left (left panel) or to the right (right panel)* B. *Vestibular stimulation by sinusoidal stimulation in darkness (maximum velocity 28°/s at 0·05 Hz) Calibration applies to right eye only.*

normal. It was also noted that there was severe scarring of the conjunctiva and Tenon's capsule as a result of previous surgery. After a limbal incision and careful dissection the site of the left lateral rectus was carefully inspected. Despite a thorough search deep into the orbit no lateral rectus muscle was seen (Fig. 4). Inspection of the medial rectus muscle revealed a very thin, atrophic muscle, on which a 6 mm resection was performed. Postoperatively there was practically no change in either the deviation of the eye or the head posture.

Methods

The procedure for recording and analysis of eye movements has previously been described.[8] Tönnies equipment was used for both optokinetic and rotatory stimulation. Saccade velocity and acceleration profiles were calculated from monocular eye positions sampled at 250 Hz during a 20° horizontal calibration of saccades by means of a method of numerical smoothing and differentiation.

Results

With forced fixation in the primary position case 1 displayed dysconjugate nystagmus with divergent fast phases (Figs. 5A, B). The nystagmus increased in intensity on gaze to the right and was virtually absent on gaze to the left. Spontaneously left gaze up to 20° was achieved through a compensatory torticollis. In case 2 a similar nystagmus was noted in primary gaze. As in case 1, the nystagmus increased on gaze to the right, but there was no neutral zone. In complete darkness no spontaneous nystagmus occurred in either patient.

We used evoked nystagmus to find out which eye was correctly controlled by the ocular motor plant in the brain stem. In both patients this appeared to be the right eye, for with this eye both the slow and the fast phases of optokinetic and vestibular nystagmus were in the expected direction (Figs. 6A, B). On the other hand the left eye moved in the opposite direction, that is, it adducted when the right eye adducted and abducted when the right eye abducted. Adduction in the present context implied only a medially directed movement, since in both patients adduction of the left eye beyond the midline was lacking. Vertical optokinetic nystagmus was normal in both patients.

Voluntary saccade analysis was possible only in case two (Figs. 7A, B). Correct calibration was feasible for the right eye only; the calibration value was assigned also to the left eye channel because in

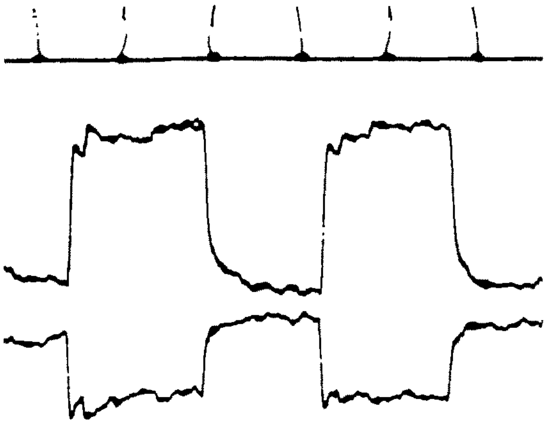

Fig. 7A

Fig. 7 *Voluntary saccade testing, case 2.* A: *Electro-oculographic recording, the position step of the right eye (2nd tracing from top) presumably is 20°*

monocular viewing the left eye could not attain an amplitude of 20°. Abduction of the right eye was normal in the sense that the velocity and acceleration profiles had the expected shapes and the saccade parameters were within normal limits.' On the assumption that calibration is also applicable to the left eye, adduction of both eyes was slow, that of the left eye being more severely impaired. The appearances of the saccade profiles resembled that encountered in cases of bilateral internuclear ophthalmoplegia (INO). This applied particularly to the acceleration profiles.

During intense fixation both patients had saccadic back-to-back oscillations. This interesting phenomenon was more prominent in the right eye of case 2. This eye showed frequency sweeps, that is, a progressive increase of frequency of saccades reaching a frequency of 12 Hz. The saccadic frequency increase was associated with a decrease in amplitude (Figs. 8A, B).

Discussion

As reviewed in Table 1, congenital adduction palsy with synergistic divergence is usually noted during

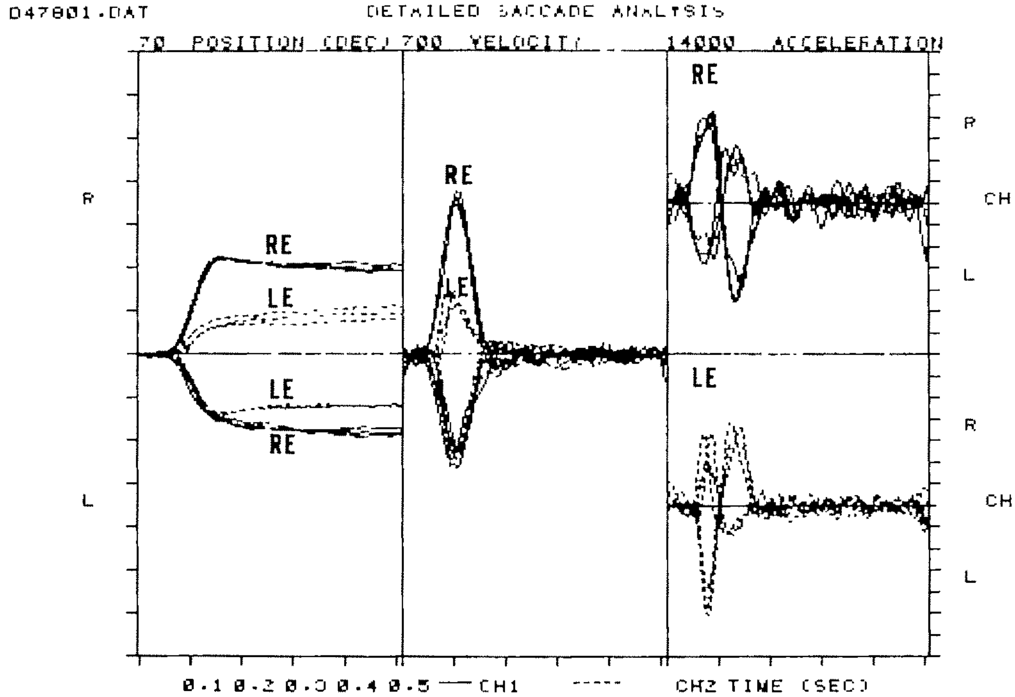

Fig. 7B

Fig 7 B *Superposition display of 20° saccades for right eye (CH1) and left eye (CH2) Correct calibration applies to the right eye only (see text). Adduction is clearly impaired in both eyes relative to abduction. Allowing for an overall filter effect of approximately second-order low-pass with a cut-off frequency of 15 Hz, the maximum abduction velocity of the right eye is normal*

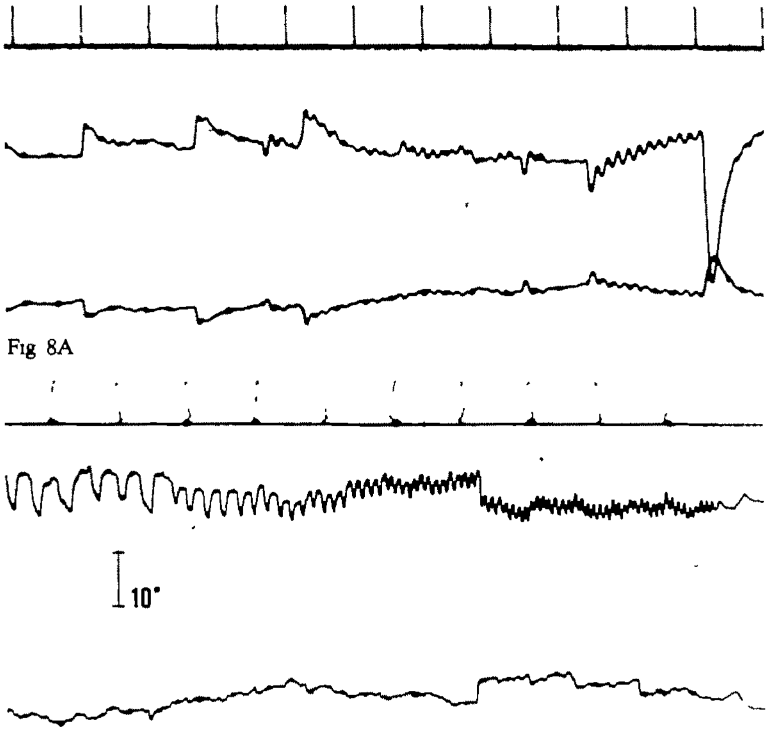
Fig 8A

Fig. 8B

Fig. 8 *Electro-oculographic recordings during intense fixation in case 1* (A) *and case 2* (B). *Note back-to-back saccadic oscillations especially in case 2, which also shows a frequency sweep of saccades*

childhood as an adduction deficit, involving the left eye in 75% of the cases, and associated with synergistic divergence during attempted adduction of the apparently paretic eye. In the primary position there is always an exotropia of the affected eye and, in three of the 11 reported cases, a spontaneous abduction nystagmus. Evoked inverse nystagmus of the affected eye has been demonstrated in all cases tested. The disorder shows a moderate male preponderance.

The clinical findings in our two cases conform to this presentation. However, to the best of our knowledge our case 2 is the first patient in whom arthrogryposis multiplex has been recorded as an associated congenital disorder. Arthrogryposis multiplex is, on the other hand, seen with the Möbius syndrome,[10] a disorder which shows a close relationship to Duane's retraction syndrome both in pathogenesis,[11 12] and in its association with segmental developmental anomalies.[13] Our second patient is also unique in the sense that synergistric divergence was noted both clinically and electro-oculographically, and yet at subsequent surgical exploration the lateral rectus muscle was found to be absent. Although it is most likely that this was a case of a 'lost muscle' following the first surgical intervention, it is also equally clear that the observed synergistic abduction did not result from lateral rectus muscle innervation alone. We believe that in this case the abduction movement was carried out as a secondary action of the inferior rectus and/or inferior oblique muscles. We draw our assumption from anatomical evidence[14] and from evidence derived from two histopathologically examined cases of Duane's retraction syndrome, in which anomalous innervation between the oculomotor nerve and the lateral rectus muscle has usually involved the inferior division of the oculomotor nerve.[15 16] Such a mechanism is in accord with the innervational hypothesis advanced to explain synergistic divergence.

Previously the apparent medial rectus muscle palsy was attributed to internuclear ophthalmoplegia or selective destruction in the medial rectus muscle nucleus, whereas the abduction movement was attributed to anomalous connections between the abducens nuclei.[2 3] Our electro-oculographic study of these two patients showed impairment of adduction associated with bilateral abduction nystagmus, and the affected eye showed an inverse nystagmus during optokinetic and vestibular testing. We were unable, however, to demonstrate dysmetric waveforms of the abducting saccades.[8 17] It seems unlikely therefore

Table 1 *Congenital unilateral adduction palsy and synergistic divergence*

Authors	*Patients sex and age*	*Primary position*	*Adduction palsy*	*Synergistic divergence*	*Evoked nystagmus*	*Associated features*	*Aetiology Proposed mechanism for divergence*
Bárány[1]	F, 3	±Straight, bilateral abduction nystagmus	Left eye	On right gaze	Inverse in LE	—	Birth trauma connections of L+R nucleus VI
Worth and Chavasse[2]	M, 3	Exotropia left eye	Left eye	On right gaze	—	—	Medial rectus palsy allows superior+inferior oblique to abduct the eye further
Burian and Cahill[3]	M, 5	Exotropia left eye	Left eye	On right gaze	Inverse in LE	—	Anomalous innervation
Burian *et al.*[4]	F, 9	Exotropia right eye	Right eye	On right and left gaze	Covergent nystagmus	Mental retardation	Related to Duane's syndrome
Znajda and Krill[5]	M, 4	Exotropia left eye	Left eye	On right gaze	—	—	Congenital anomaly of innervation
Wilcox *et al.*[6]	M, 7	Exotropia right eye	Right eye	On left gaze	Inverse in RE	—	Related to Duane's syndrome
Wagner *et al.*[7]	F, 5	Exotropia left eye	Left eye	On right gaze	Inverse in LE	—	Variant of type 2 Duane's syndrome
	F, 8	Exotropia left eye	Left eye	On right gaze	—	—	
	M, 4	Exotropia right eye	Right eye	On left gaze	—	—	
Cruysberg *et al.* (present study)	F, 4	Exotropia left eye, bilateral abduction nystagmus	Left eye	On right gaze	Inverse in LE	—	Related to Duane's syndrome. Oculomotor innervation intended for the medial rectus muscle supplies the lateral rectus muscle and other extraocular muscles
	M, 23	Exotropia left eye, bilateral abduction nystagmus	Left eye	On right gaze	Inverse in LE	Arthrogryposis multiplex congenita	

that internuclear disturbances were responsible for these patients' movement disorder. This is corroborated by the finding that the adduction had a normal duration, whereas in internuclear ophthalmoplegia it is significantly prolonged.

Wilcox *et al.*[6] studied by electromyography a case of congenital adduction palsy with synergistic divergence. They found that limitation of adduction in their patient resulted from anomalous and greater innervation of the antagonistic lateral rectus muscle. This mechanism placed this disorder in the same category of innervational disturbances as Duane's retraction syndrome. Like Huber's[14] Duane type II case, failure of adduction was regarded as the major defect. However, in the present cases, instead of retracting on adduction the eye moves further into abduction.

Wilcox *et al.*[6] proposed an innervational mechanism whereby the abducens nerve was supposed to be either hypoplastic or absent and most of the oculomotor innervation intended for the medial rectus muscle supplied the lateral rectus muscle. The motor supply to the medial rectus muscle arises from the inferior branch of the oculomotor nerve, which also innervates the inferior oblique and the inferior rectus muscles. This anatomical fact would explain the maintenance of synergistic divergence by the inferior muscles in the absence of the lateral rectus muscle, as noted in our second patient.

In this patient, the slowing of adduction of the left eye is sufficiently explained by the finding of a thin, atrophic medial rectus muscle, but the apparently similar slowing of adduction observed in the right eye calls for another explanation. It might be that, on the right side also, some of the innervation intended for the medial rectus muscle aberrantly reaches the inferior oblique and the inferior rectus muscles. This would then result in cocontraction impairing the adduction of that eye to some extent, but apparently less than in the left eye.

Because synergistic divergence shows such close relationship to Duane's retraction syndrome, it should also be considered a developmental anomaly characterised by absence of the abducens nucleus and subsequent innervation of the lateral rectus muscle by the inferior branch of the oculomotor nerve,[15 16] probably owing to a teratogenic disturbance during the second month of pregnancy.[19]

High frequency saccadic oscillations with back-to-back saccades occur in voluntary nystagmus[20] and in ocular flutter,[21] an ocular movement disorder indicating pontine-cerebellar dysfunction. The occurrence of these movements in both our patients may be interpreted as an indication of the brain stem origin of their movement disturbance. However, it is also possible that the saccadic oscillations are actually a type of fixation instability caused by the peculiar innervation which results in conflicting retinal information being sent to the brain.

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Fibrinous iritis due to oxybuprocaine

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SUMMARY Following minor surgery performed under topical application of oxybuprocaine (Dorsacaine, Novesin) two patients suffered from fibrinous iritis and moderate corneal swelling. We believe that this represents a toxic reaction caused by an inadvertent entry of this drug into the anterior chamber during the procedure.

Oxybuprocaine or benoxinate (Dorsacaine, Novesin) is a topical local anaesthetic which is widely used in diagnostic and surgical procedures in the eye. It is considered to be well tolerated, with only minimal side effects, mainly ocular discomfort (stinging) and punctate corneal epithelial damage.[1-3] We report on two patients who developed fibrinous iritis and moderate corneal swelling which we attribute to the instillation of oxybuprocaine during surgery. This side effect of the drug has not been reported elsewhere.

CASE 1

A 61-year-old man underwent an uneventful intracapsular cataract extraction with implantation of an anterior chamber lens (Kelman-Multiflex) in his right eye. On the fourth postoperative day a slight dehiscence of the limbal wound accompanied by hypotony was noted. The anterior chamber was deep, with a minimal cellular flare. Firm patching of the eye over two days was ineffectual and the wound was resutured. Under topical 0·4% oxybuprocaine (Novesin) the fornix-based conjunctival flap was lifted and three loose corneoscleral 10-0 nylon sutures were replaced. Oxybuprocaine had to be instilled several times during the operation, so that direct contact of the drug with the iris was unavoidable. No other drug was administered during the procedure, and the anterior chamber was allowed to reform spontaneously. The conjunctival flap was then fixed with one 8-0 Vicryl suture, an antibiotic-corticosteroid ointment was applied, and the eye was patched. Some hours later the patient complained of pain in his eye and forehead, which could be relieved by analgesics.

Next morning examination of the eye disclosed ciliary injection and slight corneal swelling. There was a fibrinous exudate in the anterior chamber, and focal iridovitreal adhesions had formed. The intraocular pressure was 19 mmHg, and vision was reduced to 0·08. The eye was treated with mydriatics and local corticosteroids, 8 to 10 times daily. Within five days the fibrinous exudate resolved and vision improved to 0·65.

CASE 2

A 64-year-old woman underwent an uneventful extracapsular cataract extraction in her right eye, with implantation of a C-loop posterior-chamber lens. On the day of her discharge (fourth postoperative day) she was found to have zero pressure in her operated eye owing to a wound leak. The anterior chamber was deep, with minimal cellular flare. A firm pressure dressing was tried for two days, but without any effect, and resuturing of the dehiscent incision was performed. Under topical anaesthesia with 1·0% oxybuprocaine (Novesin) the fornix-based conjunctival flap was lifted and loose sutures were replaced. As in the first case the oxybuprocaine had to be instilled during the operation, and contact with the iris could not be avoided. The anterior chamber was reformed with balanced salt solution. No other drug was used during the entire procedure. After suturing of the conjunctival flap a steroid-antibiotic ointment was applied and the eye was patched.

Some hours later severe eye pain developed which radiated into the entire side of the head. Analgesics were given but gave only minimal relief. When the eye was examined 10 hours after the procedure, it was severely injected and photophobic. The corneal epithelium was oedematous, and the anterior chamber contained a massive fibrinous exudate. There were focal adhesions of the iris to the intraocular lens. The intraocular pressure was 21 mmHg

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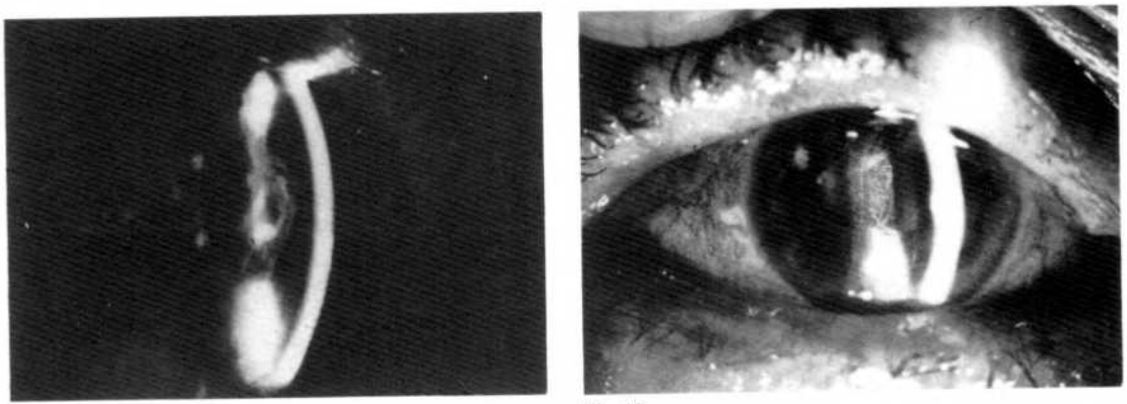
Fig. 1A Fig. 1B

Fig. 1 *Fibrinous exudate on first day* (A) *and second day* (B) *after treatment. Note residual posterior synechia at 6 o'clock.*

and vision was reduced to hand movements. Therapy consisted of acetylprednisolone (1% solution applied topically every hour) and maximal mydriasis. The fibrinous exudate resolved gradually within one week (Figs. 1A, B), and vision was ultimately restored.

Discussion

Oxybuprocaine is an effective, well tolerated surface anaesthetic which has been widely used in ophthalmology for about 30 years. Whereas an initial stinging sensation and corneal epithelial changes are probably the only side effects known to be caused by a 0·4% solution,[1,2] nothing is known about probable toxic effects of this drug if it inadvertently enters the anterior chamber. Injections of local anaesthetics into the anterior chambers of animals are usually damaging, particularly to the corneal endothelium.[4,5] In one patient an accidental injection of amethocaine into the anterior chamber caused severe injury, ending with bullous keratopathy, permanently dilated pupil, and focal iris atrophy. In the present two cases 0·4% and 1·0% solutions of oxybuprocaine were applied to repair minor corneoscleral wound leaks, and no other drug was administered. However, this drug appears to have inadvertently entered the anterior chamber while being instilled during the operation. Shortly after the procedure, both patients presented with similar changes, mainly corneal clouding and fibrinous iritis.

For several reasons we attribute this inflammatory condition to the local anaesthetic: (1) During the entire procedure, no other drug was used which might have elicited such a reaction. (2) Generally, preoperative application of 0·4% oxybuprocaine is adequate to allow the repair of slight wound leaks without further complications. In these two cases, however, additional oxybuprocaine had to be given during the procedure, so that some entered the anterior chamber. (3) The severity of the inflammatory response correlated well with the concentration of the drug instilled—that is, the 1·0% concentration caused a much severer reaction than did a lower concentration.

We therefore conclude that oxybuprocaine, if inadvertently allowed to enter the anterior chamber, may cause fibrinous iritis and corneal swelling.

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Book reviews

Clinical Light Damage to the Eye. Edited by DAVID MILLER. Pp. 225. DM. 178.00. Springer-Verlag: Berlin. 1987.

This is a book I would love to say I enjoyed reading—but I did not. Its problems start with the title, which conveyed to me the impression that I was going to discover within its covers the eye damaging potential of exposure to various types of clinical instruments incurred during examinations, operations, or therapeutic procedures. This, however, is not the case, as the book is really a pastiche of subjects vaguely related to light and its potentially harmful effects, written by a number of authors of varying style, interest, and expertise. Its lack of objectivity and or logic is further highlighted by a glance at the titles of its four major subdivisions These are· the nature of light and light damage to biological tissues; light damage to the eye; protecting the eye from light damage, and finally, and somewhat obscurely, an overview of light damage to the eye. This last section, though one of the best, almost seems an afterthought occasioned by a guest author responding to a late invitation. While I am sure this is not the case, it is the impression gained by reading the title and the volume of material repeated in this section that appears elsewhere in the book.

I certainly feel that this book addresses a subject that needs critical attention by clinical audiences in view of the current trends in using both specialised and intense sources of optical radiation for diagnosis and therapy throughout ophthalmology. Unfortunately I think that these authors have not fulfilled their self appointed task In part I suspect that this is because the pressures of modern publishing have not allowed them to view each other's contributions and, on reflection, delete repetitions and attend to group omissions Multiauthored texts of this type need far firmer editing than this volume has received

The initial section on light is an excellent idea and at its best when discussing philosophical aspects of optical radiation and its interactions with various biotic and inanimate systems within the biosphere. It is least helpful, however, when it should be most practical, that is, in trying to explain to non-physicists the problems of measuring light sources and defining the dose delivered to the biological target. Further, it should be far more comprehensive in explaining the confusion that exists as a result of experts in this field using two systems of measurement—radiometric and photometric. This is a perennial area of misunderstanding and confusion, and although some attempt is made to address the problem it lacks comprehensibility, and most of all it lacks explicit diagrams.

A systematic approach is also lacking in the treatment of the interactions of light and the eye. I think it would have been helpful to review briefly the concepts of transmission, scatter, and absorption of radiation and from this basis discuss the spectrum of incident radiation presently at each of the media or tissues within the globe. Having related these data the authors would have provided helpful orientation by giving some indication of action spectra of induced effects due to endogenous pigments Finally I would like to have seen an overview of the mechanisms by which light may damage tissues and in particular a clear recognition of the distinctions between photothermal and photochemical damage. In contrast the synergistic interactions between these two mechanisms in relation to damage induced by high irradiance clinical sources such as operating microscopes would also have been helpful. This topic is not emphasised in the text, and, although the wavelength dependence of photochemical damage is indicated, it is emphasised in the ultraviolet, with respect to the lens, but not in the blue region of the visible spectrum, where we are now aware of the well characterised 'blue light hazard' for the retina.

Instead of a panoramic approach the book jumps directly from light to tissues, and for some obscure reason leaps straight to the angle As an informed reader I commend the authors for including it as a sector of the globe usually ignored in texts on light induced damage, but why before the cornea, lens, or retina? Surely in these latter structures the basic principle of photon-tissue interactions are far better understood and more easily explained than in the trabecular meshwork.

The section on retina and its aging process is a highlight but again is marred, this time by the poor quality of the illustrations. Throughout the book the colour plates are not of high quality and some are very poor indeed.

In summary this book was a disappointment to me, but I am sure it will grace many book shelves, as it is a useful source of reference material. JOHN MARSHALL

Manual of Cataract Surgery. By ROBERT M SINSKEY and Jay V PATEL. Pp. 88. £24.95. Churchill Livingstone: Edinburgh 1987.

This is one of a series of manuals in ophthalmology produced by Churchill Livingstone and the principal author, Robert Sinskey, is an internationally renowned cataract surgeon. The first four of his 12 chapters deal with general considerations of anaesthesia, instrumentation, and preoperative preparation. The last chapter is concerned with postoperative care, and the intervening seven chapters deal with the various aspects of the surgery itself. Separate chapters are devoted to incisions, anterior capsulotomy, planned extracapsular extraction, posterior chamber phacoemulsification, the insertion of the intraocular lens, prevention and management of complications, and closure of the wound The text of each chapter is divided into short, lucid sections, and the layout with plenty of headings of bold typeface and many uncluttered line drawings makes the manual easy to use.

Inevitably with descriptions of precise surgical techniques any reviewer is unable to agree with everything that is described, but the manual serves the purpose of giving a clear account of how to manage a cataract by extracapsular means in a way which should keep a beginner out of serious difficulties. Sinskey is most renowned for phacoemulsification, and it is therefore not surprising to find that of this short book the largest chapter deals with posterior chamber phacoemulsification. The opening sentence of the chapter describes the technique as 'the method of choice for cataract extraction'. Clearly that comment continues to be arguable.

If one has any complaint about this chapter it is that the description of the technique of phacoemulsification makes it seem far simpler to carry out than it is in practice. The chapter on intraocular lens implantation deals only with the lens of Sinskey style. Apart from the Sinskey lens, the Sinskey forceps and Sinskey hook also feature in the text at this point

As the preface indicates, this book has been written for a surgeon beginning surgical training, and as a clear account of extracapsular cataract technique it serves this purpose nicely.

ARTHUR D MCG STEELE

Progress in Clinical and Biological Research. Vol 247. Degenerative Retinal Disorders: Clinical and Laboratory Investigations. Eds Joe G Hollyfield, Robert E Anderson, Matthew M LaVail. Pp. 606. US$ 98.00. Liss: New York. 1987.

This volume is the latest in a series which publishes the proceedings of the Symposia in Clinical and Biological Research. It covers the proceedings of a symposium on retinal degeneration held in Japan in September 1986. It is divided into three sections, the first of which deals with retinitis pigmentosa and other inherited retinal degenerations in man. Because of the time lag in publication much further basic research has occurred and been published since the symposium was held, and the section, while covering the latest developments up to 1986, is deficient in the latest genetic studies, particularly in retinitis pigmentosa. Most of the section deals with retinitis pigmentosa, but the coverage, as one might imagine, is patchy

The second section deals with inherited retinal degenerations in laboratory animals and would be of great use to those who might become involved in animal research in this field, since it outlines 10 different animal models in six different species This section is well written and provides very helpful background information for researchers in the field.

The last section deals with induced retinal degenerations in laboratory animals, mainly in relation to the toxicity of light and taurine deficiency Again, this section is patchy, but the papers in it are of a high quality.

The volume as a whole suffers from differences in typeface between papers and indeed different types of paper within the volume also, giving it a curiously unprofessional air and a lack of literary continuity It is expensive and of limited value except to those in the field and, in particular, workers involved in animal model research.

A L CROMBIE

Uveitis: A Colour Manual of Diagnosis and Treatment. By Jack J Kanski. Pp. 114. £29·50. Butterworth: Guildford. 1987.

Jack Kanski is now the most versatile and prolific ophthalmic author since Sir Stewart Duke-Elder. This latest book is a further product of his co-operation with Butterworths and is beautifully produced. The binding is good, paper excellent quality, illustrations lavish, the colour photographs superb, and the layout clear and pleasing.

A short book of just over 100 pages, it starts with an introductory chapter on definitions, classification, and physical signs of uveitis and then divides specific conditions into groups, each of which forms a chapter These are arthritic syndromes, non-infectious systemic disease, chronic systemic infections, parasites, viral and fungus infection, common idiopathic uveitis, and rare idiopathic syndromes, with the final three chapters on treatment, cataract surgery, and glaucoma.

The text is aimed at resident level The descriptions of syndromes are brief and subdivided into symptoms, signs, differential diagnosis, treatment, etc, which makes the description clear and concise but does not lead to any discussion. A feature of the book that I found slightly irritating was a catch phrase or important clinical point put in a box as a 'note' Although these highlight interesting or important points, they give the text a rather glib appearance and in some ways detract from its seriousness. This is a didactic book. Suggestions for further reading rather than references are given in each chapter There is little or no discussion, so that it is sometimes difficult to place observations on clinical features or management into clinical context. Some growing points in uveitis such as seroconversion of toxoplasmosis during pregnancy or the management of patients on cyclosporin are hardly mentioned, and immunology is mentioned only where it has a diagnostic relevance; this illustrates how little it contributes to the management of routine patients

The book aims to provide a good solid clinical basis for junior doctors interested in uveitis, and in this role it is probably the best available.

DAVID SPALTON

Radial Keratotomy: Surgical Techniques. Edited by Donald R Sanders. Pp. 137 £45.00. John Wiley: Chichester. 1986.

This small hard cover book by six authors, apart from the editor, is designed to describe a number of simple approaches to incisional refractive surgery, for the management of both myopia and astigmatism.

The text is divided into three sections, each of two chapters The first section deals with spherical correction by radial keratotomy using single depth incisions The second section deals with spherical correction by radial keratotomy using multiple depth incisions, and the third outlines incisional approaches to the correction of astigmatism The authors, all American, are well known for their interest in refractive surgery and they present their subject, presumably under the guidance of good editing, in a clear and uncomplicated manner The text is illustrated with black-and-white photographs and uncluttered drawings

This book illustrates most effectively the extraordinary variability of this procedure in the hands of different practitioners, and each of the authors reaches the inevitable conclusion that the procedures described will achieve different results in different hands. It is therefore somewhat tiresome to find that some of the authors have been tempted to include pages of individual results of surgical procedures The author has hoped when doing this to illustrate the value of his own adjustments and modifications, but for the reader, particularly one who may be inexperienced in refractive surgical techniques, the data are more confusing than helpful Despite this quibble, however, I found the book valuable and would certainly recommend it to readers keen to expand their knowledge of these techniques

ARTHUR D MCG STEELE

Macroscopic Ocular Pathology: An Atlas Including Correlations with Standardized Echography. By F H Stefani and G Hasenfratz. Pp. 178. DM 240.00. Springer Verlag: Berlin. 1987.

Professor Stefani's object in preparing this atlas of the macroscopical appearances of eye diseases was not to present a comprehensive textbook of ocular pathology, but rather to supplement those which exist in order to provide a more complete gallery of colour pictures of the morbid anatomy of the globe than is to be found even in the most erudite manuals wherein clinical, histological, and ultrastructural appearances are usually featured. He has succeeded admirably The illustrations are of the highest quality, and the accompanying text and legends are factual, concise, and correct. It is not to be expected in a work of this kind that aetiological theories would be discussed or references quoted, but a list of relevant textbooks is given. Dr G Hasenfratz has contributed a chapter on standardised echography and its techniques, together with typical echograms to complement certain illustrations. This beautifully produced atlas should find a useful place in the library and the laboratory

NORMAN ASHTON

Neovaisseaux Sous-Retiniens Maculaires et Laser. By G Coscas and G Soubrane. Pp. 228. 240F. Doin Editeurs: Paris. 1987.

In 1985 a conference was held in Paris on subretinal neovascularisation at the macula and laser treatment. This book is the product of the meeting, and it contains useful information on this important topic. In particular, it summarises the considerable achievements of the group in Créteil, who have provided us with a great deal of information on the natural history of subretinal neovascularisation in its various settings Of considerable value are the contributions on occult neovascularisation. It is now evident that this presentation of new vessels is common, and yet little has been published on the behaviour characteristics of these lesions

This volume represents a considerable achievement by Drs Couscas and Soubrane, and the book contains a great deal of information.

ALAN C BIRD

Notes

Panhellenic congress

The 22nd Panhellenic Ophthalmological Congress will be held in Athens, Greece, on 25–28 May 1989. The main topics of the congress will be. (*a*) complications of intraocular lens implantation, (*b*) macular diseases. Further information from the President, Professor John Koliopoulos, Secretariat of the 22nd Panhellenic Ophthalmological Congress, 10 Loukianou Street, 106 75 Athens, Greece

Prevention of blindness: research grants

The British Council for Prevention of Blindness was formed in 1976 to promote the prevention of blindness, and is affiliated to the International Agency for Prevention of Blindness, which operates in 60 countries Applications for grants, normally not exceeding £10 000 a year are considered by the council, which meets in January, May, and September. Applications should define carefully their relevance to the prevention of blindness, their objectives, research design and methodology, intended duration, and details of expenditure under various headings The council aims to extend and not to duplicate the sight-saving efforts of other organisations and therefore needs to know whether applicants have sought help from other bodies, even unsuccessfully It is intended to support UK and foreign projects on a roughly 50/50 basis Projects which have a low relevance to a substantial cause of blindness will not be supported. Applications should be made on a standard form obtainable from the Director, David Chesterman, British Council for Prevention of Blindness, 12 Harcourt Street, London W1H 1DS, and should reach him by 10 April, 10 August, and 10 December in any year, six weeks before the relevant Council meeting.

College of Ophthalmologists

The inaugural congress of the college will be held on 3–7 April 1989 at the Queen Elizabeth II Conference Centre, near Westminster Abbey, London. Registration fee £200 before 15 March 1989, £225 thereafter. Official language English Mr John Scott (Cambridge) will give the Duke-Elder lecture. Applications to present a free paper and all inquiries to: Miss Margaret Hallendorf, College of Ophthalmologists, Bramber Court, 2 Bramber Road, London W14 9PQ.

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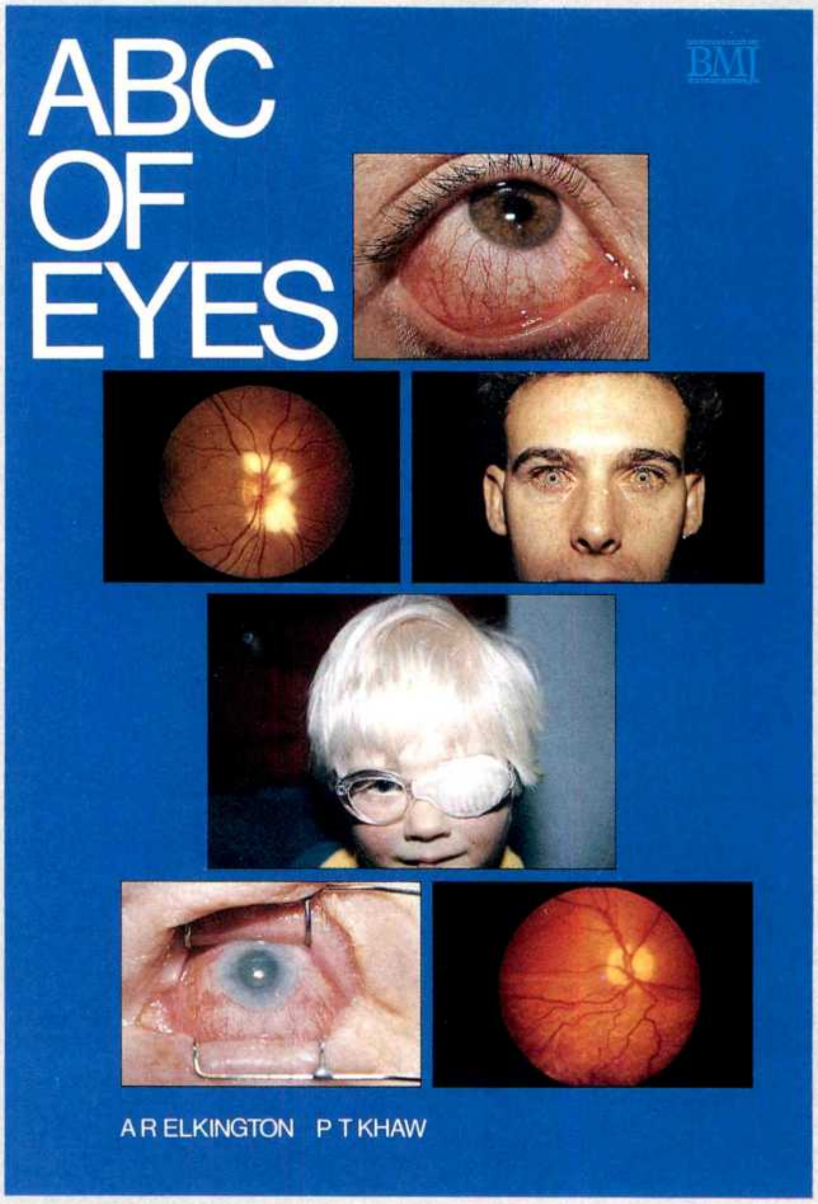

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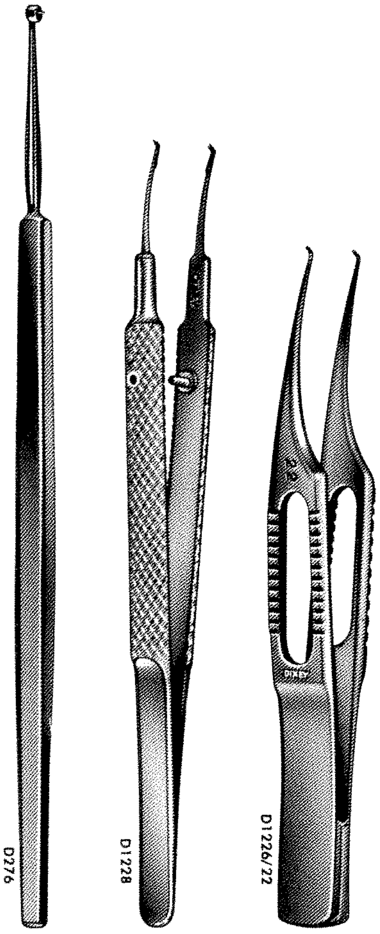

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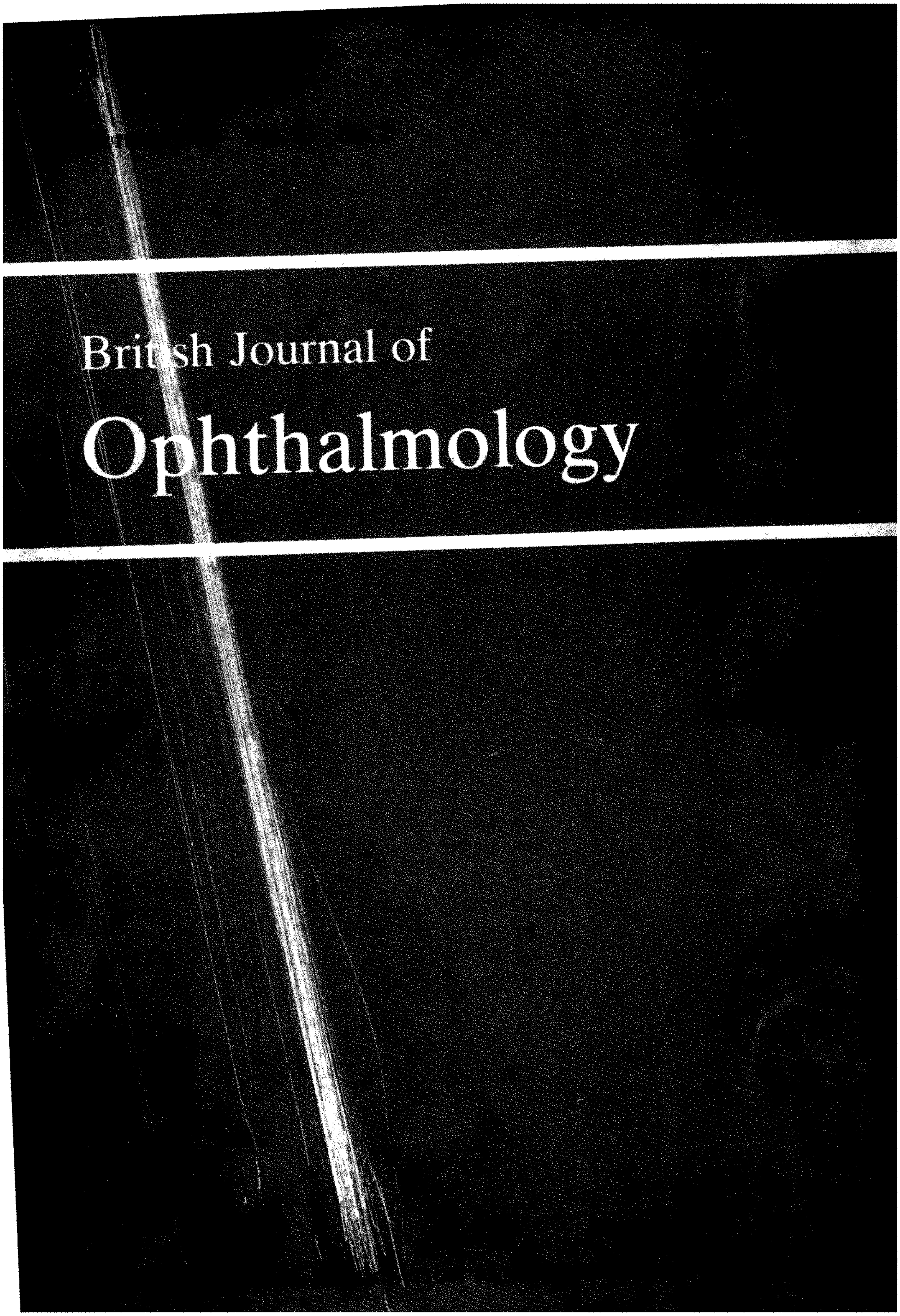

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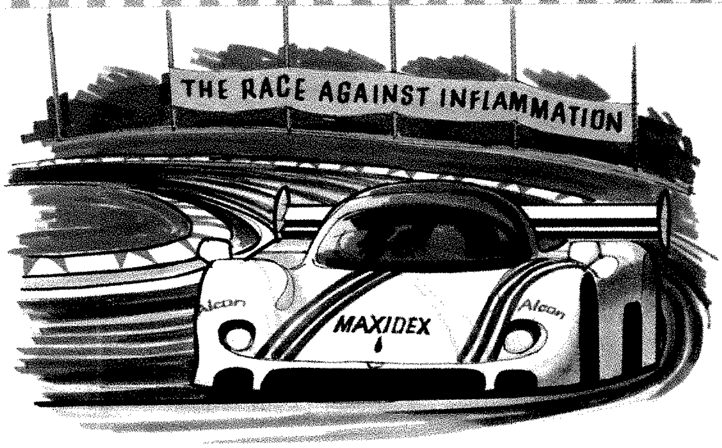

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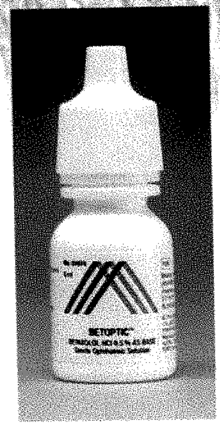

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British Journal of Ophthalmology, 1989, **73,** 81

Editorial: Blindness in two worlds

In this issue we publish three surveys of blindness, one from the Gambia and two from the United Kingdom. As might be expected there are great differences between the two. Strict comparison is difficult because the African and UK studies were carried out differently, the former being a prospective clinical study of actual patients in a sample of the population but the latter an examination of Blind Certificates. Nevertheless in spite of this difference it is still possible to perceive dissimilarities between the pattern of blindness in Africa and in the UK.

The two principal features of interest in such surveys are, first, the number of blind persons as a proportion of the population (the 'burden of blindness'), and secondly the causes of the blindness. The Gambia differs from the UK in both respects.

So far as the Gambia is concerned the prevalence of blindness is estimated to be 0·7% of the population (of 800 000). Unfortunately it is not possible to compare this with anything in the present UK figures, since they are quoted in terms of annual incidence of blind registration, but it is known from other studies that the prevalence of blindness in the UK is 0·18%.[1] When it is considered that the average age of the population in the Gambia is probably lower than that of the UK (though this figure is not quoted in the present papers) the difference becomes even more emphatic. It is not without significance, one would think, that the periurban area of Banjul in the Gambia showed much less visual impairment than the poorer slum area of the capital, where the prevalence was similar to that in the rural areas. One would expect that the principal causes of differences between the Third World and the UK would rest on economic grounds, so that it is interesting to have this internal confirmation.

The principal causes of blindness in the Gambia in numerical order are cataract and uncorrected aphakia 55%, non-trachomatous corneal opacity and phthisis bulbi 20%, trachoma 17%, and all other causes 8%. Glaucoma accounted for only 2%, but the authors believe this may be an underestimate, since their study did not include visual fields.

It is noticeable that macular degeneration makes no impact whatsoever on the blind statistics of the African study and that the overwhelming burden comes from cataract and corneal disease. It is probable that as antibiotics gradually become more available (one hopes) that the burden of corneal blindness will be reduced in time. Unfortunately the same cannot be said for cataract, and although there have been useful recent investigations into the possible causes of cataract, linking it in particular to diarrhoea,[2] there is as yet no real prospect of preventing it. Thus until more surgery can be delivered to the underdeveloped countries, there is no hope of the cataract burden being reduced.

Compared with the Gambia we in the UK are in clover. Our cataract burden has been reduced to an astonishing degree, not only in contrast to the state of affairs in Africa but also in 1985 compared with 1959.

There is one particularly disappointing statistic, however, and this concerns glaucoma. In Table 11 of the Avon study it can be seen that the 'all ages' incidence rate per 100 000 population has worsened between 1959 and 1985 from 2·60 to 4·70. However, the age-banded rate for 60–69 shows an improvement from 5·20 to 2·80, whereas the rate for the 70+ group shows a deterioration from 30·90 to 37·0. The 'all ages' rates may simply be reflecting a change in the age make-up of the population—an increasing number of old people producing an increasing number of cases of glaucomatous blindness.

However, the statistics from Leicester show an increase in blindness from glaucoma in the age groups 65 and over during the last 20 years, from 18 per 100 000 in 1965 to 29 per 100 000 in 1985. Thus when both sets of UK statistics are taken together it remains uncertain whether there is any actual change in the incidence of blindness from glaucoma.

REDMOND J H SMITH

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British Journal of Ophthalmology, 1989, **73**, 82–87

National survey of blindness and low vision in The Gambia: Results

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From the [1]Royal Victoria Hospital, Banjul; the [2]International Centre for Eye Health, Institute of Ophthalmology, London; and [3]Pieds Nus, Caubon St Sauveur, Duras 47120, France

SUMMARY A population based survey of blindness and eye disease has been conducted throughout the whole country of The Gambia, and 8174 people were examined. The prevalence of blindness (best acuity less than 3/60) was 0·7% and low vision (6/24–3/60) 1·4%. The causes of blindness were cataract (55%), non-trachomatous corneal opacity/phthisis (20%), and trachoma (17%). An estimated 5500 people in The Gambia require cataract surgery, 4600 eyelid surgery for entropion, and 4600 people spectacles to correct a refractive error which causes a visual acuity of less than 6/18. More than half the current burden of blindness in The Gambia is potentially remediable through the provision of cataract surgery and aphakic spectacles.

The Gambia is a small country of approximately 800 000 people situated on the west coast of Africa. A population based survey of blindness and eye disease has been conducted throughout the whole country, initiated by the Ministry of Health in The Gambia, in collaboration with the International Centre for Eye Health, London, and the Prevention of Blindness Programme of the World Health Organisation.

The survey was undertaken as part of the first phase in the development of a National Eye Care Programme in order to establish baseline data on the prevalence of the major blinding diseases. This information will assist in the planning and future evaluation of eye services and blindness control programmes.

Material and methods

The Gambia is divided into three administrative health regions—Western, Central, and Eastern. A population based prevalence survey of blindness and eye disease was conducted during March-May 1986 on a countrywide sample of approximately 1% of the total population (Fig. 1).

A multistage cluster random sampling procedure was used with stratification by (1) district, subgrouping north and south of the river; (2) urban, periurban, and rural communities; and (3) settlement size (under 300 and 300 or more).

The only exclusion area was part of the periurban area of the capital, Banjul, which is inhabited by foreigners with high incomes. A poor slum area, and a typical periurban area of the capital were surveyed. The 1983 census figures for The Gambia provided the sampling frame for the study. Fifty two communities were randomly chosen to reach the required sample size of at least 8000. The sample provided 8696 persons, of whom 8174 were examined.

Data were collected by means of the Eye Examination Record (Version II) developed by the World Health Organisation Prevention of Blindness Programme. This form was evaluated by the team as part of the study. Two teams worked side by side, with each team consisting of an ophthalmologist, ophthalmic assistant, one general nurse, two eye auxiliaries, two enumerators, and a driver. Demographic data were recorded by the enumerators, visual acuities measured by the eye auxiliaries, and ocular examination, including assessment for trachoma (all ages) and xerophthalmia (0-6 years), performed by the ophthalmic assistants and ophthalmologists. Any individual with a visual acuity of less than 6/18 in either eye was examined by the ophthalmologist, and the cause of low vision (6/24–3/60) or blindness (less than 3/60) was recorded. Any action required (medical treatment, surgery, or spectacles) as identified by the examination team was also recorded. Further details on the project outline, design and

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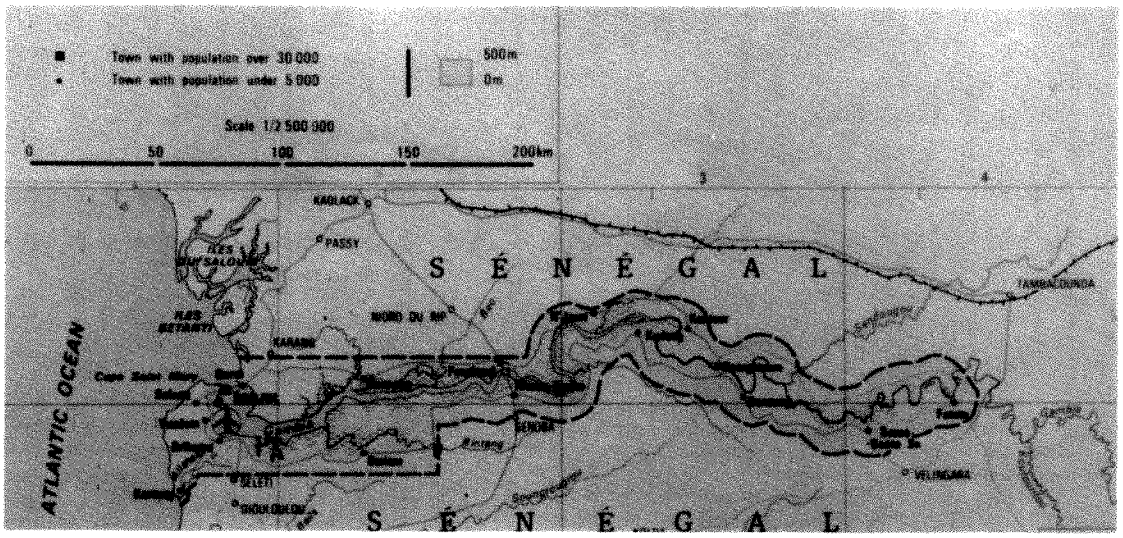

Fig. 1 *Map of The Gambia.*

methodology of the survey, and evaluation of the eye examination record are given elsewhere.[1,2]

Results

Table 1 gives data on the census population and coverage of the required sample, which ranged from 86% in the capital to 97% in the Eastern region, with an overall coverage of 94%.

The data estimated the prevalence of blindness defined as a binocular visual acuity of less than 3/60 to be 0·7% (5500 people in The Gambia) and prevalence of low vision (best acuity 6/24–3/60) to be 1·4% (11 000 people in The Gambia). The total number of blind and visually impaired was 16 500 (approximate 95% confidence limits 14 000–19 000). The prevalence of blindness by age in The Gambia is given in Fig. 2, but the figures do not account for blind children who might have been staying in blind schools.

The periurban area of Banjul shows much less visual impairment and blindness than the poorer slum area of the capital. The prevalence of blindness and low vision in the rural areas is similar to that in the poor urban area of Banjul (Fig. 3).

Unoperated cataract was responsible for 45% of the blindness in The Gambia and 57% of low vision. Uncorrected aphakia was the cause of 8% of blindness and 10% of low vision. Two per cent of the blindness was due to irreversible blindness from neglected cataract or from the complications of traditional cataract surgery (couching), so that a total of 55% of blindness (Fig. 4) and 67% of low vision (Fig. 5) could be attributed to cataract and its complications.

The prevalence of blindness from cataract was minimal in Banjul and in its periurban population. In the sample from these areas no blind person was found that required cataract surgery or aphakic correction, suggesting that these communities were well served by present services being offered by the Eye Department at the Royal Victoria Hospital, Banjul.

Table 1 *National survey of blindness and eye disease, The Gambia 1986*

Region	*Population*	*Number examined*	*Coverage*
Eastern	282 000	2606	97%
Central	136 000	2812	96%
Western			
Banjul	50 000	412	86%
Districts	332 000	3140	90%
Total	800 000	8174	94%

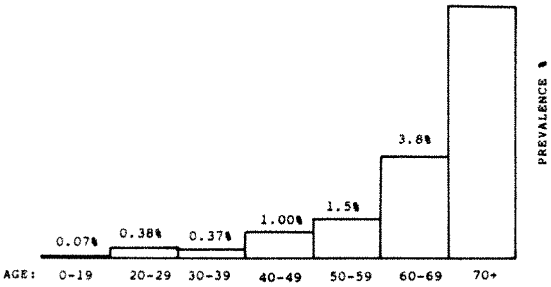

Fig. 2 *Prevalence of blindness by age: The Gambia, 1986.*

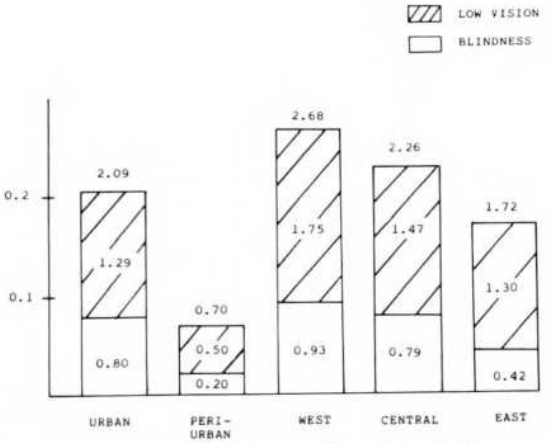

Fig. 3 *Prevalence of blindness and low vision in five areas of The Gambia, standardised for age and sex.*

Trachoma was responsible for 17% of the blindness (Fig. 4). The risk of blindness and low vision from trachoma was more than three times higher in females than males (Table 2). The prevalence of trichiasis and entropion varied from 0·6% in the periurban area of Banjul to 1·8% in the rural Western Health District.

Non-trachomatous corneal opacity and bilateral phthisis bulbi were responsible for 20% of the blindness (Fig. 4). (This group excludes people with trachomatous corneal opacity or phthisis due to trauma.) It was not possible certainly to attribute any of the corneal blindness to vitamin A deficiency, though this was a possibility. The prevalence of Bitot spot formation (XIB) in children under 6 years of age was approximately two per 1000.

The survey data estimated 2% of blindness and 1% of low vision in The Gambia to be due to glaucoma. The prevalence of chronic glaucoma was 0·2% in people over 40 years of age. However, the true prevalence of glaucoma was probably much higher, as visual assessment in this survey was based only on visual acuity and did not take into account assessment of visual field.

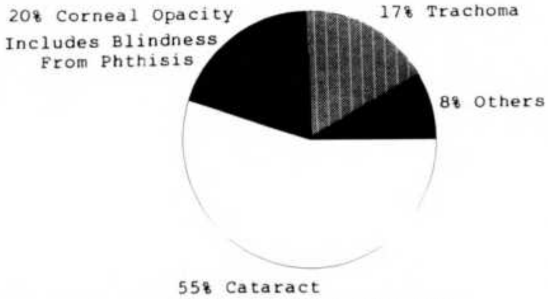

Fig. 4 *Causes of blindness in The Gambia, 1986.*

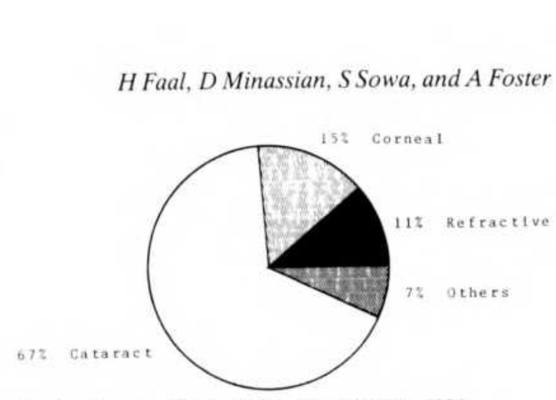

Fig. 5 *Causes of low vision in The Gambia, 1986.*

6% of the blindness was due to other causes including optic atrophy, retinal diseases, and trauma (Fig. 4). 11% of low vision was due to refractive errors which were potentially remediable (Fig. 5).

The age standardised prevalence of visual loss (blindness and low vision) was 1·6% in men and 2·5% in women (M:F 1:1·6) (Table 2). The excess visual loss in females could be attributed mainly to cataract and trachoma. The data supported the evidence that males were more likely to seek surgical treatment and aphakic correction for their cataract than females.

Cataract was responsible for nearly half the cases of unilateral blindness and corneal scar for 16% (Fig. 6). 5% of the population (40,000 people) were blind in one eye. The prevalence of uniocular blindness in children (0–14 yr) was 0·3% (estimated 1200 children in The Gambia). Corneal opacity and phthisis bulbi accounted for 70% of children with uniocular blindness (Fig. 7).

The eye examination record included information on what kind of treatment, if any, was required by the population sample. These data allowed an estimate to be made of essential ophthalmic services in The Gambia (Table 3).

Discussion

The 94% overall coverage rate of a randomised cluster sample allows reliable estimates for the prevalence and causes of blindness and low vision in

Table 2 *Age standardised prevalence of visual loss by cause*

	Prevalence in females	*Prevalence in males*	*Prevalence*	
			Ratio	*Difference*
Trachoma	0·20%	0·057%	3·51	0·14%
Cataract	0·94%	0·690%	1·36	0·32%
Uncorrected aphakia	0·15%	0·086%	1·74	0·064%
Other corneal	0·10%	0·057%	1·75	0·043%

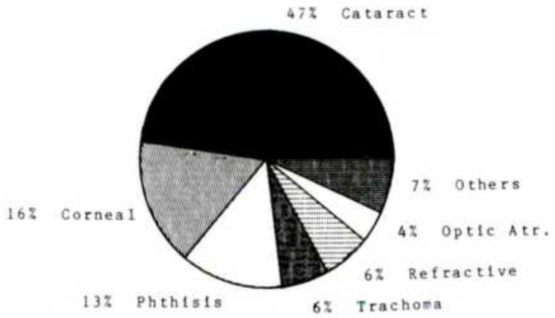

Fig. 6 *Causes of uniocular blindness in The Gambia, 1986.*

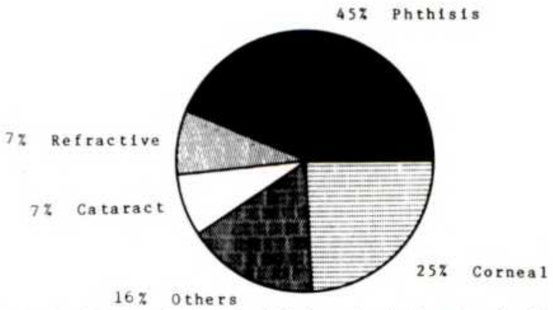

Fig. 7 *Causes of uniocular blindness in children (under 15 years) in The Gambia, 1986.*

The Gambia. This is the first such national survey undertaken in Africa. The results are consistent with similar surveys undertaken in parts of Malawi[3] and Kenya.[4]

The Gambia with a population of just under a million and one ophthalmologist provides a suitable model for many countries in sub-Saharan Africa, in which there is on average one ophthalmologist per million population.[6]

The Gambia does not have the special ophthalmological problems found in some areas of West Africa where onchocerciasis is endemic and responsible for a large proportion of blindness. Trachoma, although responsible for 17% of blindness in The Gambia, is not the hyperendemic disease that is seen in many arid parts of Africa. The data from The Gambia therefore demonstrate the pattern of eye problems that are seen in African countries which have limited health services and ophthalmological care.

CATARACT

Cataract is the single most important cause of blindness and low vision. An estimated 5500 patients require cataract surgery in The Gambia, but the annual cataract extraction rate is less than 300 operations per year. At present there is one full-time ophthalmologist in The Gambia with occasional support from visiting Chinese or Western ophthalmologists. Dealing with the problem of cataract blindness will require three to four permanent 'cataract surgeons.' The possible alternatives are to train Gambian ophthalmologists, to teach medical practitioners how to perform cataract surgery, or to train ophthalmic assistants as cataract surgeons. One ophthalmic assistant has already been trained in cataract surgery, and a Gambian doctor is now to start training as an ophthalmologist.

Uncorrected aphakia is responsible for 8% of blindness and 10% of low vision. It is essential that, as blind people with cataract receive their operation, facilities are also available to provide at least basic spherical aphakic spectacles. At present there is one optical workshop in the capital, Banjul, producing spherical aphakic spectacles. It is planned that this workshop will be expanded to deal with the increased need. As more ophthalmic assistants are trained and posted to the district hospitals in rural areas, they will be provided with aphakic spectacles from the optical workshop in Banjul for distribution to post-cataract patients.

Table 3 *Summary of the need for basic ophthalmic services in The Gambia*

	Estimated number of people in need of treatment
Cataract surgery	5500
Eyelid surgery	4600
Need spectacles (distances)	4600*
Medical eye treatment	83 000
Other surgical or medical treatment	6500

*Does not include presbyopes who may need spectacles for close work, or the estimated 5500 people who will need glasses after cataract surgery.

These numbers represent the current backlog of people in need of the basic eye care.

TRACHOMA

Trachoma is responsible for 17% of blindness. The prevalence of visual loss from trachoma in women was 0·20%, which is 3·5 times higher than that in men of the same age. An estimated 4600 patients require surgery for entropion. There are no accurate figures on how many operations are being done each year at present, but it is almost certainly well below 500 a year. The training of eye nurses and ophthalmic assistants in one appropriate operation for upper eyelid entropion could do much to reduce the prevalence of visual loss from trachoma in the future. Two ophthalmic assistants have already been trained to perform entropion surgery, and it is planned to train more in the future.

NON-TRACHOMATOUS CORNEAL SCAR

On the assumption that bilateral phthisis bulbi is a result of bilateral corneal ulceration and not bilateral trauma, then non-trachomatous corneal scar/phthisis was responsible for 20% of blindness in adults. Seventy per cent of uniocular blindness in children in the survey was due to corneal scar or phthisis. There were too few children blind in both eyes to give data on the causes of bilateral blindness, but a subsequent examination of 14 children at the blind school in Banjul showed four cases to be due to bilateral corneal scarring. It is not possible from the data to determine accurately the aetiological factors leading to corneal ulceration and blindness in these two groups, but measles, vitamin A deficiency, the use of harmful traditional eye medicines, and ophthalmia neonatorum are the most likely causes of bilateral ulcers; and trauma, herpes simplex, and bacterial and fungal infection are likely to be responsible for the majority of the uniocular corneal scars.

The reduction in blindness from corneal ulceration requires action at the level of maternal and child health services to increase measles vaccination, improve child nutrition, and avoid the use of harmful traditional medicines by ensuring that safe eye medicines such as tetracycline eye ointment are readily available to the population.

Medical workers need to be trained in the diagnosis and urgent management of corneal ulceration in children and adults. The training of community health nurses in activities to prevent trachoma and corneal blindness started in May 1987 and is planned to continue. The training includes the diagnosis and treatment of acute red eye, as well as promotive and preventive measures to improve eye health. Further work is required on the relevant importance of trauma and traditional eye medicines in causing bacterial and fungal suppurative keratitis.

OTHER CAUSES

Glaucoma was responsible for only 2% of the blindness and 1% of low vision. However, this is undoubtedly an underestimate, as the survey examination assessed visual loss only in terms of reduced visual acuity without systematic measurement of visual field in the sample population. But this figure is much less than the findings from previous studies in Nigeria 20%, Kenya 12%, and Tanzania 14%.[4,6,7] The reasons for these differences are not known, though genetic factors may be important.

A substantial proportion of low vision in The Gambia (11%) is due to uncorrected refractive errors. This cause of visual loss is potentially remediable by the provision of appropriate optical services. An estimated 4600 people need spectacles for distance correction because their visual acuity is less than 6/18. The majority of these people (90%) live in rural communities. This does not include people requiring aphakic or presbyopic corrections.

Other causes of blindness and low vision include trauma, which was responsible for 2% of blindness; and optic atrophy, which was responsible for 2% of blindness and 1% of low vision.

Conclusion

The Gambia, with a population of 800 000 and one ophthalmologist, provides a model for many parts of Africa, enabling us to identify the important ophthalmic problems and develop relevant eye services to reduce the number of needlessly blind people.

Cataract is the major cause of blindness (estimated 7000 people/million population requiring cataract surgery). To meet this urgent need a minimum of three to four cataract surgeons per million population is initially required in African countries.

Corneal scarring from trachoma and corneal ulceration is the second cause of blindness. These conditions are largely preventable through immunisation programmes, nutrition education, improved personal hygiene, better community sanitation, and the provision of tetracycline eye ointment and vitamin A capsules at the primary health care level.

More than half (53%) of the current burden of blindness in The Gambia is potentially remediable through the provision of cataract surgery and aphakic spectacles. 5500 people in The Gambia (7000/million population) require cataract operation.

The challenge is to develop basic curative and preventive ophthalmic services that are accessible to, and will be taken up by, the majority of the rural population. These services are now being developed and extended in The Gambia as part of the National Eye Care Programme.

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Blind and partial sight registration in Avon

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SUMMARY All blind and partially sighted registration forms for the county of Avon for a two-year period were analysed, and the findings are presented. Comparisons with the national figure published by Sorsby over 20 years ago show there has been no marked change in the rates of blind registration per 100 000 population with the exception of those for cataract, which show a large reduction. Diabetic registrations have remained similar, but this may represent an encouraging trend in view of the significant increase in the size of the diabetic population. Glaucoma may show some improvement in the future when time has elapsed for beta blockers and trabeculoplasty to be fully assessed. There has been an increase in the rate of registration from aging macular degeneration.

Since Sorsby published his extensive analyses of blindness in England and Wales[1 2] there have been major advances in patient management in ophthalmology. The most notable advances include microsurgery, fluorescein angiography, and photocoagulation, but there have been many changes in the treatment of most of the major causes of blindness. Glaucoma, cataract, aging macular disease, trauma, retinal detachment, and diabetic and other forms of retinal vasculopathy are treated in ways quite different from 25 years ago. Some disorders, such as myopia and genetic defects, remain untreatable.

This study was undertaken with three objectives: (1) to find the overall blindness rates per annum in the county of Avon; (2) to evaluate the incidence and visual disability for the major ocular diseases; and (3) to see whether the incidence of blindness and partial sightedness has altered in the past 25 years since the introduction of modern ophthalmic techniques

Precise comparison of the Avon figures with those published by Sorsby proved difficult because of the higher rate of different disorders affecting the fellow eye of registered patients (15% for Avon as opposed to 6% for Sorsby). An analysis of the information available from the registration form for individual eyes was therefore undertaken in an attempt to define more accurately the contribution of each ocular disorder to the pool of partial or complete blindness In addition this allowed an evaluation of the accuracy of whether blind or partial sight registration was correct according to the guidelines on the form, and also increased the reliability of the data to compare with Sorsby's figures.

Material and methods

All blind and partially sighted registration forms (BD8) during the two-year period 1 July 1984–31 June 1986 for the county of Avon were analysed. The registrations were divided into those fully blind and partially sighted (PS) according to the way in which the certificate had been completed by the examining ophthalmologist in section C.

As the category of blindness or PS depended on the status of the better eye, a re-evaluation of the visual handicap of all eyes for which information was available from the BD8 forms was undertaken. Details under section A (examination of the eyes) were assessed with regard to visual acuity and visual field loss, and all eyes were recategorised without reference to the information under section C. Visual acuity was classified as no perception of light (NPL), perception of light (PL), hand movements (HM), count fingers (CF), 6/60, 6/36, 6/24, 6/18, 6/12, 6/9, or 6/6. Although the guidelines on the form suggest a category of 3/60 should be employed, this was rarely used by the registering ophthalmologist and therefore was not used for the re-evaluation for this study.

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Table 1 *Number (per cent) of registrations according to age and sex*

Age	*Blind*		*Partial sight*	
	Male	*Female*	*Male*	*Female*
0–4	2 (1%)	0	0	0
5–14	2 (1%)	1	0	1 (1%)
15–19	0	2 (1%)	0	0
20–29	3 (2%)	6 (2%)	2 (2%)	2 (1%)
30–39	4 (2%)	1	3 (4%)	3 (2%)
40–49	3 (2%)	4 (1%)	3 (4%)	5 (3%)
50–59	5 (2%)	4 (1%)	5 (6%)	7 (4%)
60–64	14 (3%)	11 (3%)	6 (7%)	8 (4%)
65–69	13 (6%)	18 (5%)	5 (6%)	6 (3%)
70–79	65 (33%)	103 (27%)	32 (38%)	71 (37%)
80–84	44 (22%)	94 (25%)	13 (15%)	43 (22%)
85+	43 (22%)	132 (35%)	15 (18%)	44 (23%)
All ages	198 (100%)	376 (100%)	84 (100%)	190 (100%)

Field loss was scored in relation to the severity indicated under section A.4, that is, (*a*) nil, (*b*) less than 10°, (*c*) contracted, (*d*) central scotoma, (*e*) hemianopia, (*f*) good. Combinations of (*c*) to (*e*) were scored as (*b*). The following criteria were used, therefore, in the reassessment:

acuity less than 6/60 (regardless of field) = blind
field less than 10% (regardless of acuity) = blind
acuity equal or better than 6/60 but combination of field loss (*c*, *d*, *e*) = blind
other combinations = PS

The Avon population estimate for mid year 1985 based on the 1981 census was 942 000. In order to evaluate whether the newer ophthalmic techniques have influenced blind and PS registration, comparisons were made with the data published by Sorsby on patients registered more than 25 years ago.

Table 2 *Incidence rates (per 100 000 per year) of registrations according to age and sex*

Age	*Blind*			*Partial sight*		
	Male	*Female*	*Total*	*Male*	*Female*	*Total*
0–4	3·5	–	1·8	–	–	–
5–14	1·7	0·9	1·3	–	0·9	0·4
15–19	–	2·6	1·3	–	–	–
20–29	2·0	4·0	3·0	1·3	1·3	1·3
30–39	3·0	0·8	1·9	2·3	2·3	2·3
40–49	2·7	3·7	3·2	2·7	4·6	3·6
50–59	5·0	3·9	4·4	5·0	6·8	5·9
60–64	27·5	19·5	23·3	11·8	14·2	13·0
65–69	32·8	38·1	35·7	12·6	12·7	12·7
70–79	110·5	118·9	115·9	54·4	82·0	70·8
80–84	343·8	343·1	343·3	101·6	156·9	139·3
85+	716·7	647·1	662·9	250·0	215·7	223·5
All ages	21·7	38·7	30·5	9·2	19·6	14·5

Table 3 *Main causes of blindness and PS (total eyes after reclassification)*

	Blind	*PS*	*Total*
Aging macula	565 (49%)	234 (43%)	799 (47%)
Glaucoma	176 (15%)	40 (7%)	216 (13%)
Diabetes	71 (6%)	51 (9%)	122 (7%)
Myopia	50 (4%)	41 (8%)	91 (5%)
Cerebrovascular disease	54 (5%)	31 (6%)	85 (5%)
Optic atrophy	51 (4%)	19 (3%)	70 (4%)
Retinal vein occlusion	34 (3%)	21 (4%)	55 (3%)
Cataract (senile)	24 (2%)	30 (5%)	54 (3%)
Corneal disease (all causes)	24 (2%)	14 (3%)	38 (2%)
Retinitis pigmentosa	20 (2%)	8 (1%)	28 (2%)
Retinal detachment	16 (1%)	10 (2%)	26 (2%)
Congenital defects (including cataract)	16 (1%)	8 (1%)	24 (1%)
Amblyopia	10 (1%)	7 (1%)	17 (1%)
Others	35 (3%)	32 (6%)	67 (4%)
Total	1146 (100%)	546 (100%)	1692 (100%)

Cause not stated in four cases

Results

There was a total of 848 forms of which 574 (68%) were for blind registered patients and 274 (32%) were for partially sighted. Thus the overall blindness rate was 30 per 100 000 and the PS rate 15 per 100 000 per annum. The numbers, age, sex, and registration rates of the study population are presented in Tables 1 and 2. The main causes of blindness and partial sight after reassessment are shown in Table 3 and are related to age in Tables 4 and 5. The degree of blindness according to acuity and field loss are shown in Tables 6 and 7. Some disagreement was observed between the original assessment and the re-evaluation on visual grounds alone—Table 8. Of the 496 patients re-evaluated as blind in both eyes 28 (6%) were registered PS, and of the 130 patients considered PS in both eyes 26 (20%) were registered blind. When one eye was reassessed as blind and one PS (221 cases), blind registration was recorded in 79 (36%) rather than the theoretically correct PS, on the assumption that the patient should be registered according to the status of the better eye.

Different causes of blindness between the two eyes of the same patient were found in 15% of cases. The most common associations are listed in Table 9.

Discussion

OVERALL FIGURES FOR BLINDNESS

The incidence rates of blind registration have been based on the mid year estimates for 1985 from the 1981 census. For both males and females the incidence rate of blindness remains low until age 60, after which there is a considerable increase,

Table 4 *Age distribution of main causes of disease leading to blindness and PS after reclassification (total eyes)*

Age	*Aging macula*	*Glaucoma*	*Diabetes*	*Myopia*	*Cerebro-vascular*	*Optic atrophy*	*Retinal vein occlusion*	*Cataract*
0–4	0	0	0	0	0	2 (3%)	0	0
5–14	0	2 (1%)	0	0	0	0	0	0
15–19	0	2 (1%)	0	0	0	0	0	0
20–29	0	2 (1%)	2 (2%)	1 (1%)	0	7 (10%)	0	0
30–39	0	0	4 (3%)	2 (2%)	2 (2%)	0	0	0
40–49	0	4 (2%)	10 (8%)	0	2 (2%)	2 (3%)	0	0
50–59	6 (1%)	0	8 (7%)	6 (7%)	2 (2%)	1 (1%)	0	2 (4%)
60–64	9 (1%)	4 (2%)	20 (16%)	2 (13%)	10 (12%)	5 (7%)	1 (2%)	1 (2%)
65–69	14 (2%)	9 (4%)	27 (22%)	4 (4%)	8 (10%)	7 (10%)	6 (11%)	2 (4%)
70–79	253 (31%)	80 (37%)	35 (29%)	29 (32%)	35 (41%)	17 (24%)	20 (36%)	14 (26%)
80–84	222 (28%)	52 (24%)	11 (9%)	18 (20%)	18 (21%)	12 (18%)	15 (27%)	13 (24%)
85+	295 (37%)	61 (28%)	5 (4%)	19 (21%)	8 (10%)	17 (24%)	13 (24%)	22 (40%)
All ages	799 (100%)	216 (100%)	122 (100%)	91 (100%)	85 (100%)	70 (100%)	55 (100%)	54 (100%)

especially after age 70. Overall the incidence of blindness in females appears to be almost twice the rate in males, but in the extremely elderly (85 years and over) the rate for males is marginally higher (Table 2).

Compared with the figures published by Sorsby[1] for 1961–2 the incidence of blindness in Avon for 1985 and 1986 is similar in the younger age groups (0–30), but the numbers are small. Congenital and inherited disorders predominate, and the incidence of blindness is approximately 2·5 per 100 000. Thereafter the blindness rates quoted by Sorsby reach a higher level for each age group with the exception of males aged 60–64 (Table 10). The greatly reduced incidence of cataract registration could account for this trend.

The finding of a different cause of blindness in fellow eyes of 15% is considerably higher than the 6% noted by Sorsby. Uniocular diseases such as retinal detachment have a high incidence of different causes for the second eye, but not unexpectedly conditions producing bilateral disease such as aging macular degeneration have a low incidence of other causes of blindness in the fellow eye. The discrepancy between Sorsby's figures and ours may be partly explained by a lower incidence of cataract as a cause of registration and perhaps also by earlier detection of remediable forms of blindness, preserving useful function in one eye which later becomes affected by age related disease. The degree of blindness followed a similar pattern to what Sorsby found, though the groups were not strictly identical, as the present study did not include a category of 3/60. In this study 11% had PL or NPL (Sorsby=14%) and 69% had count fingers or hand movements (Sorsby=59%).

Ghafour *et al.*[3] published figures for blindness in the West of Scotland for the year 1980. Different age groupings were used from the present study, but the proportion of patients in the major diagnostic groups were similar. Aging macular degeneration was the

Table 5 *Incidence rates of main causes of disease leading to blindness and PS per 100 000 population per year (after reclassification)*

Age	*Aging macula*	*Glaucoma*	*Diabetes*	*Myopia*	*Cerebro-vascular*	*Optic atrophy*	*Retinal vein occlusion*	*Cataract*
0–4	–	–		–	–	0·9	–	–
0–14	–	0·4		–	–	–	–	–
15–19	–	0·7		–	–	–	–	–
20–29	–	0·3	0·3	0·2	–	1·2	–	–
30–39	–	–	0·8	0·4	0·4	–	–	–
40–49	–	0·9	2·3	–	0·5	0·5	–	–
50–59	1·5	–	2·0	1·5	0·5	0·2	–	0·5
60–64	4·2	1·9	9·3	5·6	4·7	2·3	0·5	0·5
65–69	8·1	5·2	15·6	2·3	4·6	4·0	3·5	1·2
70–79	87·0	27·5	12·0	10·0	12·0	5·8	6·9	4·8
80–84	276·1	64·7	13·7	22·4	22·4	14·9	18·7	16·2
85+	558·7	115·5	9·5	36·0	15·2	32·2	24·6	41·7
All ages	21·2	5·7	3·2	2·4	2·3	1·9	1·5	1·4

Table 6 *Visual acuity by eyes (after reclassification): incomplete information for seven registrations*

Acuity	*Blind*	*Partial sight*	*Total*
NPL	72 (6%)	18 (3%)	90 (5%)
PL	61 (5%)	15 (3%)	76 (5%)
HM	158 (14%)	44 (8%)	202 (12%)
CF	631 (55%)	97 (18%)	728 (43%)
6/60	104 (9%)	100 (18%)	204 (12%)
6/36	38 (3%)	116 (21%)	154 (9%)
6/24	15 (1%)	59 (11%)	74 (4%)
6/18	19 (2%)	55 (10%)	74 (4%)
6/12	18 (2%)	21 (4%)	39 (2%)
>6/12	27 (2%)	18 (3%)	45 (3%)
Total	1143 (100%)	543 (100%)	1686 (100%)

principal cause but formed 18% less of the total in comparison with this study. Cataract was higher by 8%, but glaucoma, diabetes, and optic atrophy were not significantly different.

OVERALL FIGURES FOR PARTIAL SIGHT

The causes of partial sight closely followed those of full registration but were approximately half as common, namely, 32% of the total. This may be a reflection of the limited social service benefits available to patients on the partially sighted register, which could also explain the relatively high number of registrations classified as blind which theoretically should have been PS. PS registration for glaucoma was proportionally less than average (19% of glaucoma registrations), whereas diabetes (41%), myopia (45%), and cataract (55%) were more than average. Ghafour *et al.* noted similar patterns, though PS registration was 45% of the total compared with 32% in this study.

A DHSS report published in 1979[4] noted a steady increase in PS registrations between 1969 and 1976. Unfortunately rates per 100 000 were not quoted except for children, and the present study contains very few registrations of young people. 'Macular lesion', cataract, and glaucoma accounted for 80% of the PS registrations listed but for only approximately 63% in this study.

Table 7 *Field of vision by eyes (after reclassification): incomplete information for 15 registrations*

Field	*Blind*	*Partial sight*	*Total*
(*a*) Nil	130 (11%)	42 (8%)	172 (10%)
(*b*) Less 10°	167 (15%)	60 (11%)	227 (14%)
(*c*) Contracted	135 (12%)	75 (14%)	210)13%)
(*d*) Central scotoma	648 (57%)	267 (50%)	915 (55%)
(*e*) Hemianopia	38 (3%)	31 (6%)	69 (4%)
(*f*) Good	22 (2%)	61 (11%)	83 (5%)
Total	1140 (100%)	536 (100%)	1676 (100%)

Combinations of (*c*), (*d*), or (*e*) were scored as (*b*).

Table 8 *Registration status compared with re-evaluation status*

Re-evaluation	*Registered*	
	Blind	*PS*
Both blind	468	28
One blind/one PS	79	142
Both PS	26	104

SPECIFIC CONDITIONS

We have compared the present figures for the leading causes of blind registration with those of Sorsby in those age groups with a high incidence (Fig. 1 and Table 11).

DIABETIC RETINOPATHY

In the past 15 years xenon and laser photocoagulation have become established as beneficial treatment for the sight threatening forms of retinopathy, namely, maculopathy and proliferative retinopathy. The current study suggests that there has been no reduction in the total registrations per 100 000 (Fig. 1a) in spite of an active therapeutic approach to retinopathy within the area of Avon. There has been an increase of 3·6 per 100 000 in the 60–69 year age group and a decrease of 4·9 in patients aged 70 or over.

It has been found that the prevalence of insulin dependent diabetics in childhood has risen greatly in the past 30 years, perhaps as much as doubling every decade.[5,6] This, together with the estimate that sight threatening retinopathy is three times more common in insulin than non-insulin dependent diabetics,[7] would suggest that the overall incidence of serious retinopathy is much higher than 25 years ago. The unchanged total diabetic registration incidence now compared with Sorsby's would indicate an encourag-

Table 9 *Numbers of eyes with different causes of blindness in fellow eyes*

	Total	*Common combinations*
Aging macular disease	49 eyes (6%)	Cataract in 9 eyes Retinal detachment 5 eyes Amblyopia 5 eyes
Venous occlusion	31 eyes (56%)	AMD 7 eyes Glaucoma 6 eyes Amblyopia 6 eyes Cataract 5 eyes
Cataract	27 eyes (50%)	AMD 9 eyes Venous occlusion 5 eyes Retinal detachment 5 eyes
Glaucoma	26 eyes (12%)	Venous occlusion 7 eyes AMD 5 eyes
Retinal detachment	23 eyes (88%)	Myopia 9 eyes AMD 5 eyes Venous occlusion 5 eyes
Amblyopia	17 eyes (100%)	Venous occlusion 6 eyes AMD 5 eyes

Table 10 *Blind registration rates per 100 000 population for Sorsby (1959–60) and Avon (1985–6)*

Age	*Males*		*Females*	
	Sorsby	*Avon study*	*Sorsby*	*Avon study*
40–49	5·1	2·7	4·4	3·7
50–59	10·0	5·0	11·4	3·9
60–64	21·3	27·5	26·6	19·5
65–69	51·6	32·8	51·5	38·1
70+	208·7	195·9	237·8	170·4

ing trend, suggesting that photocoagulation has been effective in preventing blindness in many diabetics. Whether the prevalence of non-insulin diabetes is increasing is unknown.

Although the rate of blind registration for people of working age is small, there is still a significant number of patients in middle life who require registration (Table 4). Sorsby noted a steady increase within these age groups between 1948 to 1960, but encouragingly this trend would seem to have reversed. One aspect of blindness which is not possible to ascertain from the comparative data is change in degree of blindness over the years. It is possible that navigational vision is preserved in a large proportion of diabetics which would have deteriorated to no useful vision prior to photocoagulation. In this series 122 eyes were registered as showing diabetic retinopathy. Of these, 27 (22%) had no useful vision, that is, hand movements or worse, 57 (47%) were count fingers, and 38 (31%) were 6/60 or better.

AGING MACULAR DEGENERATION

The proportion of blind registrations due to aging macular degeneration (AMD) appears to be increasing (Sorsby 1955–60: 26·9%; Ghafour 1980: 29·8%; present study 1985–6: 49%). As the majority of cases are not treatable, it might be expected that this percentage would increase as correctable forms of blindness such as cataract are prevented. Our figures may perhaps support this, but there is a very large increase in the rate per 100 000 both in the total

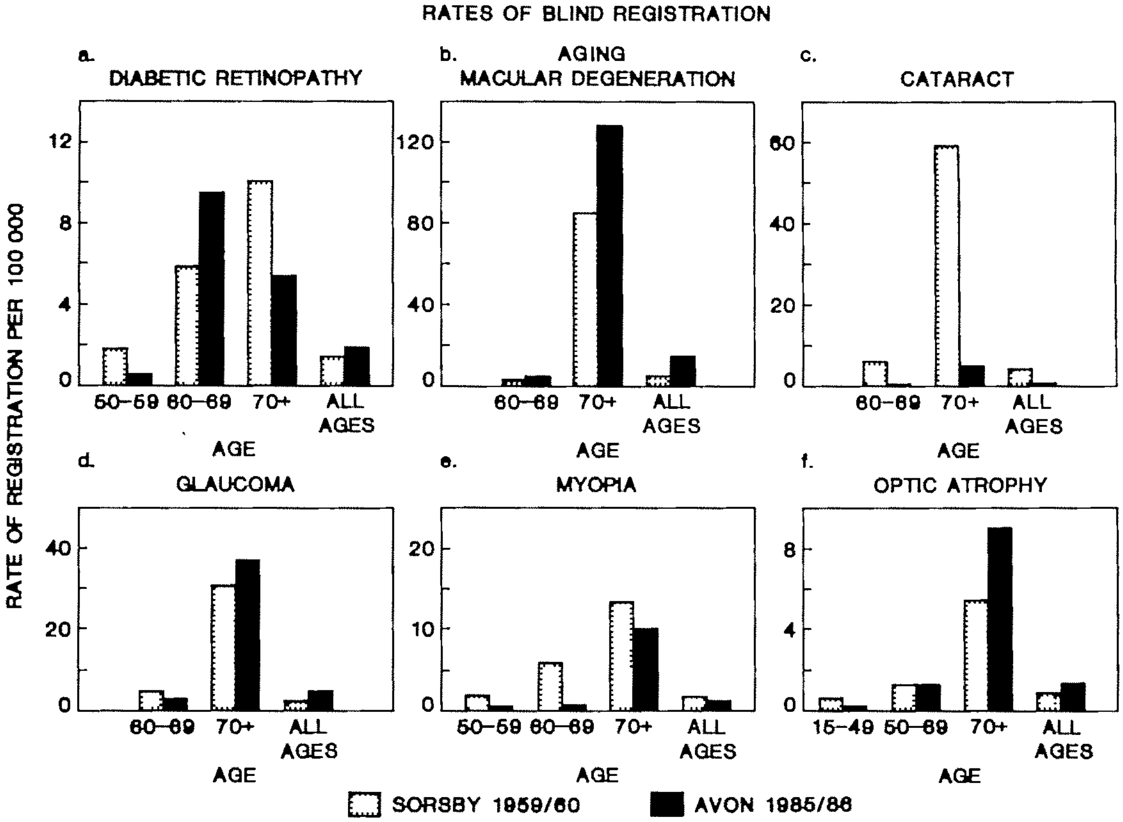

Fig. 1 *Comparison of blindness rates per 100 000 population of Sorsby (1959–60) and Avon (1985–6) age groups as in Sorsby* [12]

Table 11 *Rates of blind registration per 100 000 population for common disorders. comparison of Sorsby 1959–60 with Avon 1985–6 (age groups as in Sorsby)*

Age	*Diabetes*		*AMD*		*Cataract*		*Glaucoma*		*Myopia*	
	1959	*1985*	*1959*	*1985*	*1959*	*1985*	*1959*	*1985*	*1959*	*1985*
50–59	1·8	0·5	–	–	–	–	–	–	2·0	0·7
60–69	5·9	9·5	3·4	4·9	5·2	0·3	5·2	2·8	6·0	0·8
70+	10·1	5·2	85·0	128·0	59·7	5·0	30·9	37·0	13·5	10·1
All ages	1·5	1·9	5·7	15·0	4·7	0·6	2·6	4·7	1·8	1·3

number of registrations and for patients over 70 which cannot all be accounted for by redistribution from other causes (Fig. 1b). Increased social service support such as home help and mobility training may explain this increase.

One consultant subdivided all AMD registrations into disciform and atrophic types. From a total of 128 eyes registered in this way 35 (27%) were disciform lesions and 93 (73%) were dry geographic atrophy. Of the patients with disciform lesions 22 (63%) were blind and 13 (37%) PS and of patients with atrophic lesions 80 (86%) were blind and 13 (14%) PS. When disciform lesions were compared with geographic atrophy with regard to the degree of blindness there was no difference between the two groups. This suggests that severe macular atrophy is three times more common than disciform degeneration and produces an equal degree of visual loss. Laser photocoagulation of disciform degeneration can therefore be expected to have only a limited effect on figures for blindness from aging degeneration.

CATARACT

Cataract is the one diagnostic category to have shown a marked decrease over the years (Fig 1c). The trend outlined by Sorsby has continued, so that for the 60–69 year age group the rates per 100 000 were 11·6 in 1984, 5·4 in 1960, and 0·3 currently. In the 70+ age group the comparable figures were 82·6, 57·6, and 5·0. Factors which have contributed to this must include improved microsurgical techniques and the introduction of intraocular lenses. The latter measure has allowed much earlier intervention in the 'worse eye' before severe loss of vision bilaterally, which was necessary for aphakic spectacle wear.

GLAUCOMA

In the 60–69 year age group the downward trend in registrations has continued: 7·2 in 1949, 4·9 in 1960, and 2·8 currently. However, in spite of a greater variety of topical medications and the introduction of safer glaucoma surgery the overall figures, particularly in the 70+ age group, show there is a modest increase in the rate of registration (Fig. 1d). The great majority of registrations are in the older people and there has been no marked reduction which might have been expected with the better therapeutic methods now available. This could be explained by the fact that glaucoma is a chronic disease in many patients, with a better outlook if treated early. The newer treatments would therefore not yet be reflected in the incidence figures, on the assumption that several years elapse between diagnosis and registration. More time is needed for the full assessment of beta blockers and laser trabeculoplasty.

MYOPIA

Between 1948 and 1960 Sorsby noted a modest decrease in the rate of registration for patients less than 50 years, little change for those aged 50–69, and a slight increase for those aged 70+. Since then there would seem to have been a further decrease in all age groups, with the bulk of the registrations occurring at 70 and over (Fig. 1e), indicating blindness from myopia is related to age.

OPTIC ATROPHY

The number of patients in the present series is small but there appears to have been no significant change over the years (Fig. 1f). It may be assumed that the underlying causes such as generalised vascular disease and systemic hypertension are as common in the population as previously.

OTHER CONDITIONS

In terms of frequency of various causes of registration the 'league tables' have shown some changes in the middle order compared with Sorsby's figures. Hypertension has disappeared as a cause of blindness, but it is possible that venous occlusions may have been included in this diagnosis in the past. Iritis and retinopathy of prematurity are also less frequent causes than previously.

Retinal detachment and cerebrovascular disease, especially the latter, form a higher proportion of registrations than 25 years ago, and the figures for corneal disorders are approximately unchanged with 2% of the total. 66% of registrations are from retinal disorders and a further 17% from optic nerve disorders.

The interpretation of blind registration figures has to be cautious. The present study is over two years, with the great majority of the BD8s completed by 10 ophthalmologists. There is no obvious reason to think that Avon is not representative of the UK in general, both in terms of the resident population or of the type of medical care, but the accuracy of such a study depends on the quality of form filling. It is therefore unlikely that any figures are completely reliable, as observer variations occur. There is also some pressure to register blind rather than PS for borderline cases, as the benefits from the social services are considerably greater. It could be argued that help from the social services may be better than 25 years ago and that this would lead to an increase in the number of registrations. This could account for the larger registration rate for AMD or glaucoma, if it used to be thought that services previously were not all that helpful. This is unlikely to be a major factor, as some conditions which are largely beyond help by current medical therapy have shown no such trend—for example, optic atrophy remains static and myopia shows a decreased incidence. Care is also required in the interpretation of registration figures with regard to the prevalence of blindness in the population in general. Probably many more patients are eligible for registration than are actually recorded but are either unwilling or unlikely to be helped by registration.

By extrapolating Sorsby's blindness rates of 1959–60 and applying them to Avon in 1985–6 an extra 28 males and 74 females would have been registered blind per annum—that is, the 1985–6 rate is down 27% for males and 39% for females. The great majority of this reduction is due to the fall in cataract registrations.

The authors thank Mrs Linda Clayton for typing the manuscript and staff of DHSS, Bristol, for photocopies of the registration forms.

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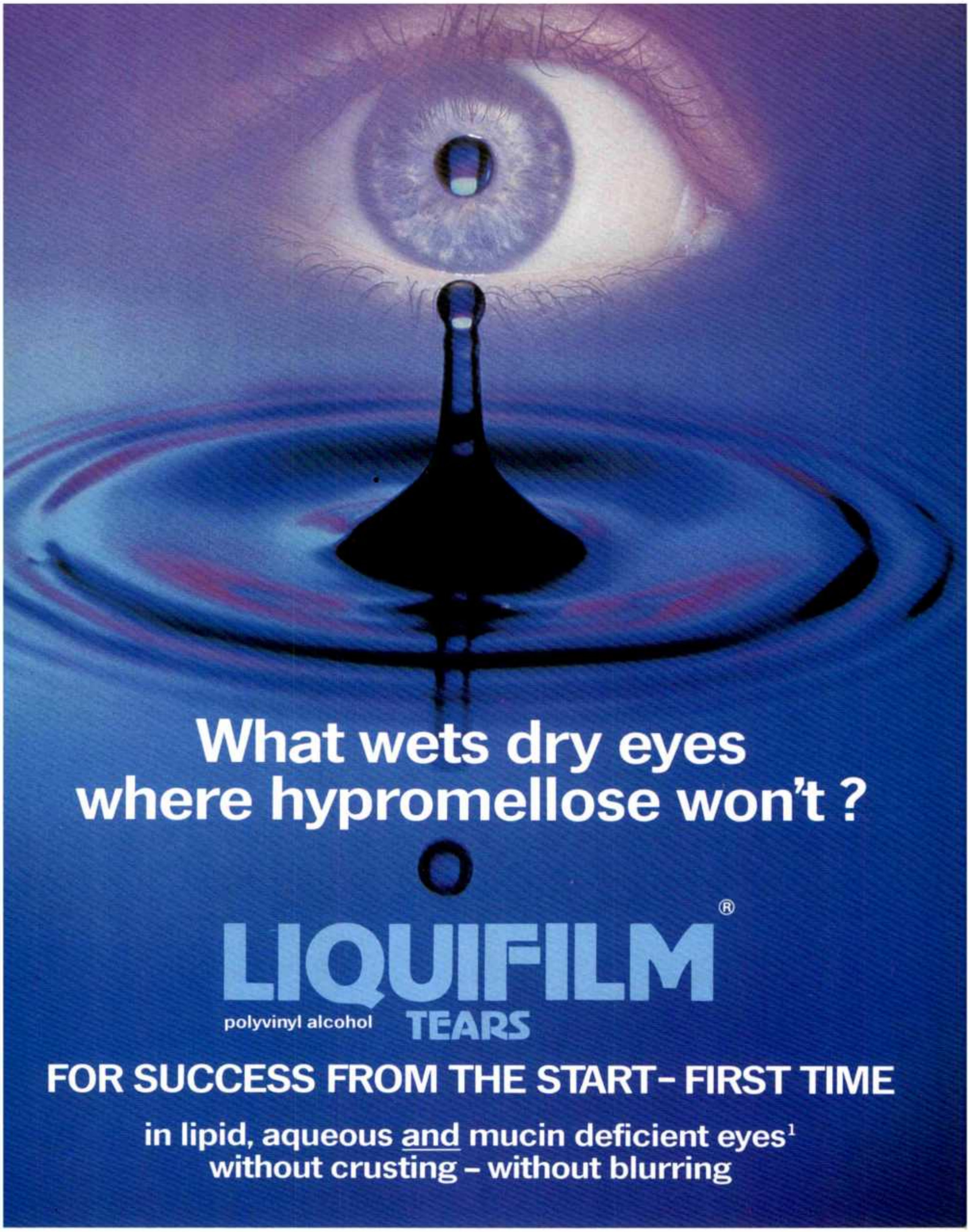
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Reference 1. Kralian LM, American Journal of Optometry and Physiological Optics 1986; **63** (No. 4): 304-308.

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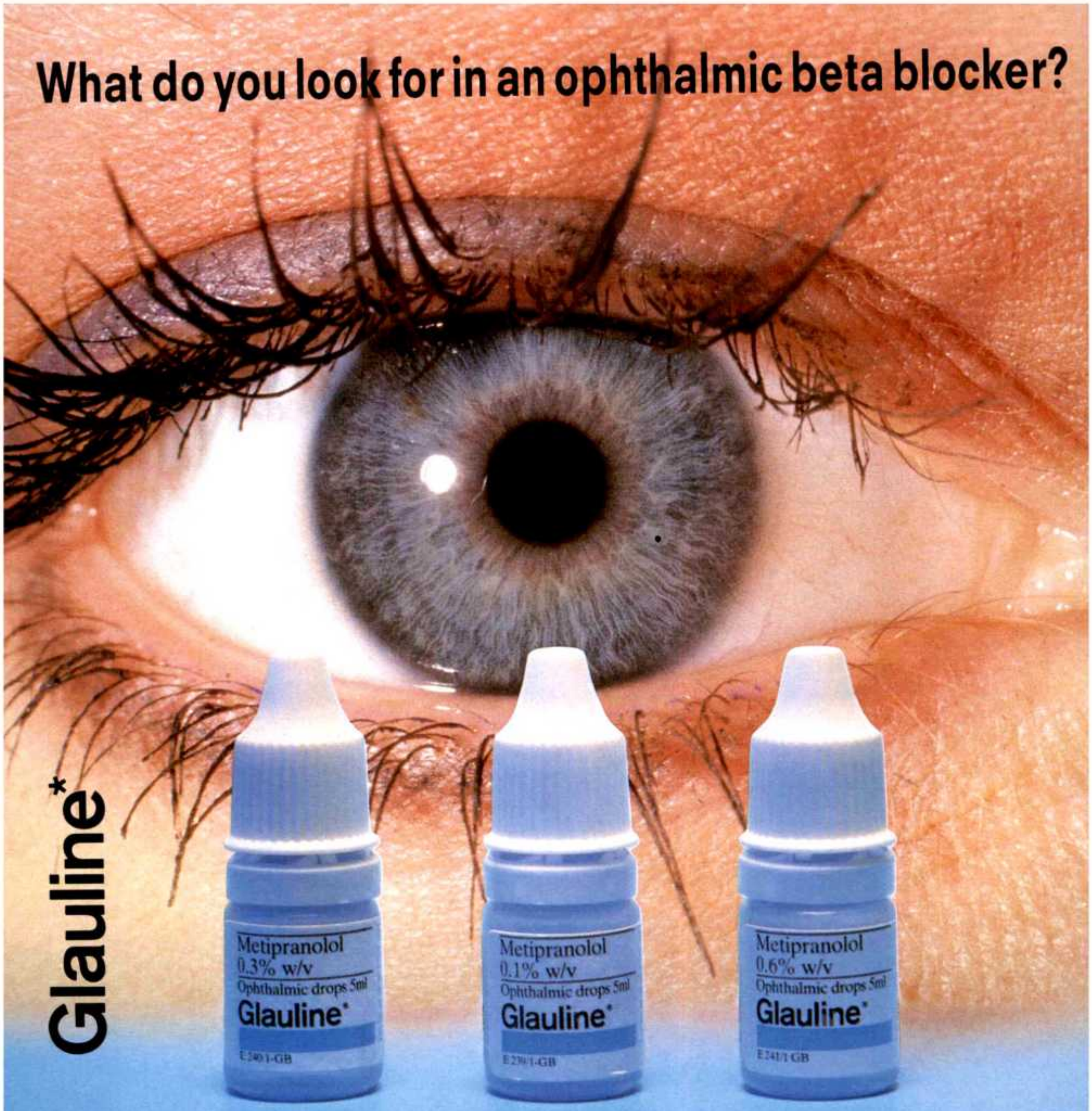

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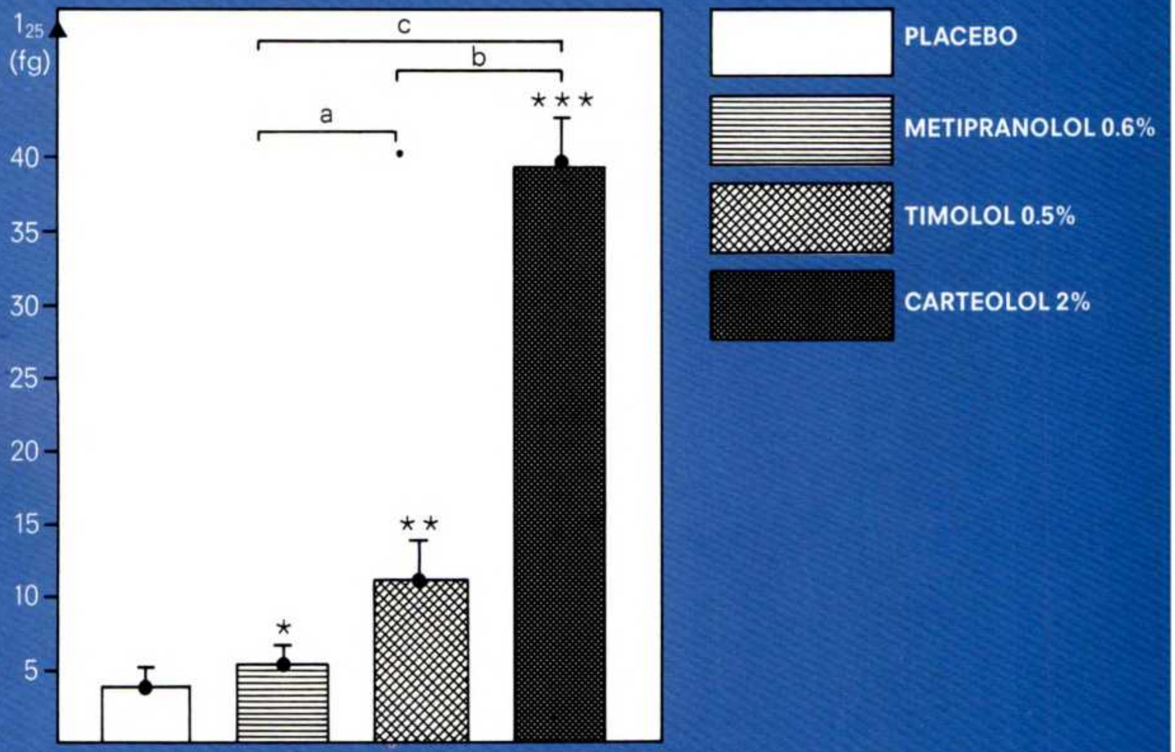

Dose of isoproterenol hydrochloride (mean ± SE) required to increase resting heart rate by 25 bpm (I_{25}) 3 hours after one drop of ophthalmic ß-blocker in each eye. (*$P < 0.05$; **$P < 0.001$; ***$P < 0.0005$ vs. placebo; a, $P < 0.02$; b, $P < 0.001$; c, $P < 0.001$.)

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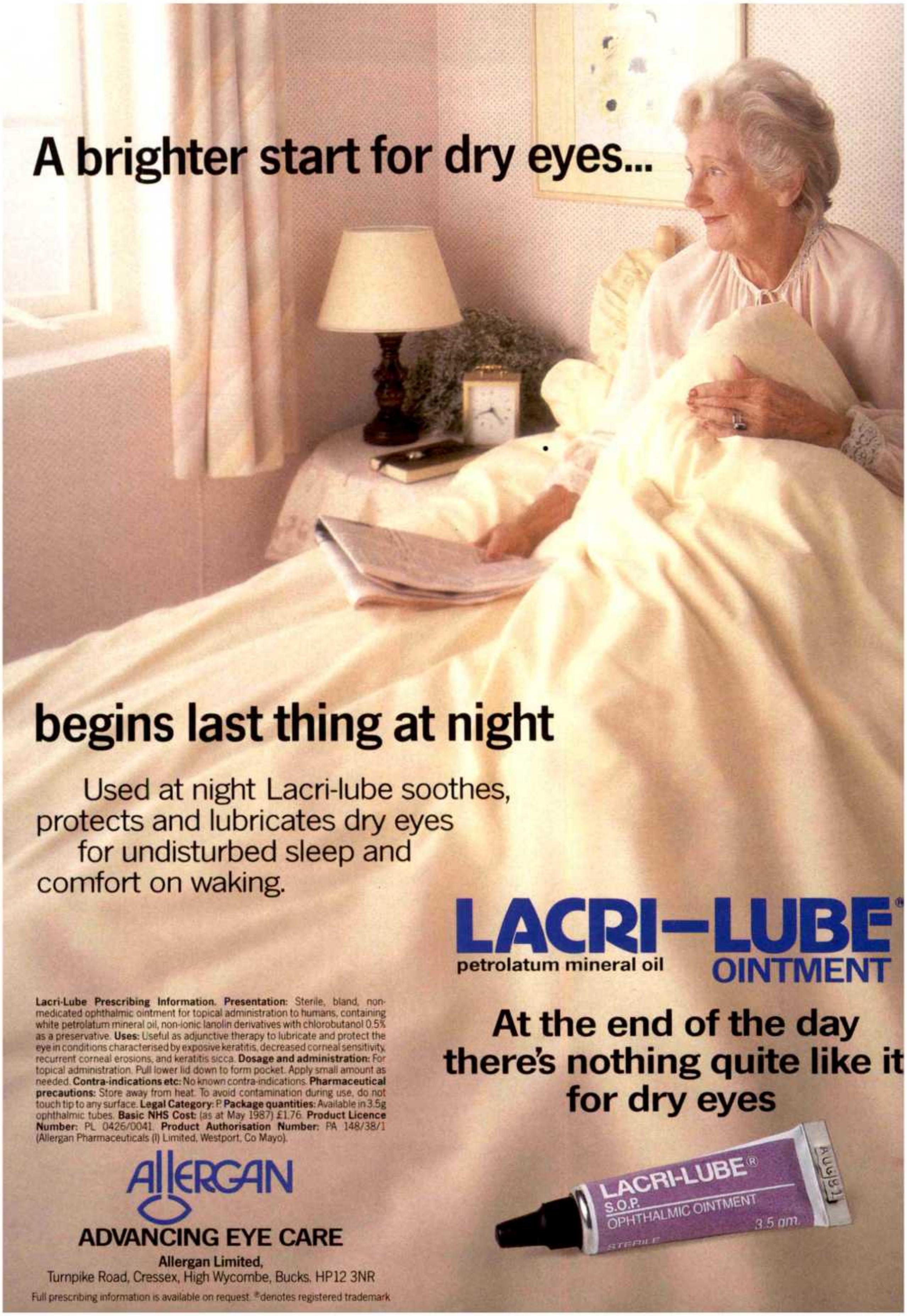

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British Journal of Ophthalmology, 1989, 73, 95–99

Recent trends in the registration of blindness and partial sight in Leicestershire

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SUMMARY A study is reported of all new registrations for blindness and partial sight in the county of Leicestershire, England, for the years 1965, 1975, and 1985. The number of new registrations for blindness has risen considerably over this period, but the increase is shown to be attributable to changes in the age structure of the population and under-registration in 1965. The number of new registrations for partial sight has also increased over the study period but by significantly more than would be expected, even after changes in the population structure are allowed for. The registration rates for Leicestershire when analysed by age, sex, and cause are shown to be broadly in line with available national figures. Registration rates for macular degeneration and glaucoma are increasing in both males and females, and rates for cataract are at a significantly higher level for women than for men.

There have been six major studies of the registration of the blind in England and Wales that together cover the period 1933–76.[1-4] Published studies since 1960 have analysed data only on those people under 65 years of age, and since the majority of blindness occurs after this age the picture given by the recent national studies is incomplete.

In order to investigate the local changes in the pattern of registration over the last 20 years and to look at registration amongst the elderly, information was obtained from the local society for the blind on all registrations in Leicestershire in each of the years 1965, 1975, and 1985. The data are analysed for differences over time due to age, sex, and cause of blindness.

In England and Wales when a person is registered as blind or partially sighted a BD8 form must be completed by a consultant ophthalmologist. In the county of Leicestershire copies of this form are sent to the local health authority, to the Department of Health and Social Security, and to the Royal Leicestershire, Rutland and Wycliffe Society for the Blind.

Persons registered as blind do not need to show a specific vision loss. Under the National Assistance Act of 1948 they need only be judged by an ophthalmologist to be 'so blind as to be unable to perform any work for which eyesight is essential'. In a similar way the Ministry of Health later advised that to be certified as partially sighted an individual must be 'substantially and permanently handicapped by defective vision caused by congenital defect, or illness, or injury'. However, the registration form does provide clear guidelines with respect to the visual acuity of a person being placed on the register. To be registered as blind an individual should have a visual acuity of at most 3/60 in the better eye, or at most 6/60 if there is marked restriction of the visual field. For partial sight registration an individual should have a visual acuity of at most 6/60 in the better eye, or 6/24 with moderate field reduction, or 6/18 with gross field reduction.

Material and methods

All BD8 forms for people first registered in 1965, 1975, and 1985 were obtained from the local society, and information was extracted on the person's age at registration, sex, status (blind or partially sighted), and the condition that led to blindness. Where more than one potentially blinding condition was noted on the form, the diagnosis judged to be chiefly respons-

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ible for the blindness was selected Because the information extracted from each form was kept to a minimum, missing data were not a problem in this study.

All people who were placed on the register for the first time in the study years and who subsequently stayed on the register were included in the analysis. Those excluded were people who moved to Leicestershire having been previously registered in another area, those who had been registered previously but who merely changed status from partially sighted to blind, and those who were registered temporarily while awaiting surgery.

Between 1965 and 1975 the boundaries of Leicestershire were altered, and all registration figures quoted have been adjusted to reflect the later borders. Population figures were similarly adjusted by means of data from various official publications.[7-10]

Where significance levels are quoted they were obtained from Poisson models for the rates, the calculations being performed by the GLIM statistical package.[11]

Results

Table 1 shows, by age group, the numbers of people registered as blind and partially sighted in each of the study years. The increasing number of total registrations over time is seen to be mainly due to an increase in registrations in those aged 75 years and over. This increase in the number of elderly people who were registered is very closely in line with the increase in the number of elderly people in the county. Table 2 displays the rates of blind registration for each age group and shows how, after allowance was made for changes in the age structure of the base population, the increase over time was much less marked.

Table 3 provides a breakdown of the blindness registration rates by age, sex, and year. Analysis of this table shows that, after adjusting for age and year, there was a significantly higher overall rate of registration among women as opposed to men (p=0·03). Similarly, if the rates are adjusted for age and sex, the figures for 1975 were significantly higher than those for 1965 (p=0·01). The adjusted rate for 1985 was a little lower than that for 1975 but not significantly so.

Table 4 gives a breakdown of partial sight registration rates by age, sex, and year. When age is allowed for, there was a significant linear increase in registration over time (p=0·001) but no significant difference between the registration rates for men and women.

Table 5 shows, for each of the three years of the study, the percentages of registrations due to each of the four major causes of blind registration in people

Table 1 *Number of people registered as blind and partially sighted in Leicestershire in 1965, 1975, and 1985 by age group*

Age	*Blind*			*Partially sighted*		
	1965	*1975*	*1985*	*1965*	*1975*	*1985*
0–4	4	4	6	1	1	0
5–14	4	2	1	4	2	4
15–29	3	11	5	1	5	2
30–44	2	9	9	3	7	4
45–64	19	30	12	15	26	26
65–74	37	57	50	24	27	56
75+	126	190	231	50	82	149
Total	195	303	314	98	150	241

Table 2 *Blind registration in Leicestershire by age group. Rates per 100 000 population*

Age	*1965*	*1975*	*1985*
0–4	6·3	6·6	10·3
5–14	3·6	1·4	0·9
15–29	2·0	5·9	2·4
30–44	1·4	5·9	5·0
45–64	10·6	16·0	6·5
65–74	66·2	82·3	72·3
75+	403·8	498·7	451·2
Overall	26·4	36·3	36·4

Table 3 *Blind registration in Leicestershire by age and sex. Rates per 100 000 population*

Age	*1965*		*1975*		*1985*	
	Male	*Female*	*Male*	*Female*	*Male*	*Female*
0–4	3·1	9·7	0·0	13·4	13·3	7·7
5–14	1·8	5·5	0·0	3·0	0·0	1·8
15–29	2·5	1·4	6·3	5·5	2·9	1·9
30–44	2·7	0·0	5·1	6·8	4·4	5·7
45–64	9·2	12·0	14·0	18·0	5·4	7·6
65–74	65·5	66·7	65·8	95·1	48·5	91·4
75+	357·8	428·6	434·4	529·0	405·7	474·8
Overall	18·3	33·8	23·3	49·0	24·2	48·0

Table 4 *Partial sight registration in Leicestershire by age and sex. Rates per 100 000 population*

Age	*1965*		*1975*		*1985*	
	Male	*Female*	*Male*	*Female*	*Male*	*Female*
0–4	0·0	3·2	0·0	3·4	0·0	0·0
5–14	3·0	3·7	1·4	2·5	3·4	3·6
15–29	1·3	0·0	4·2	1·1	0·0	1·9
30–44	2·7	1·4	5·1	4·1	3·3	1·1
45–64	4·6	12·0	12·9	14·8	14·0	7·6
65–74	17·5	60·6	39·5	38·6	74·4	86·2
75+	174·3	152·7	196·7	223·9	280·0	296·7
Overall	8·8	17·5	13·8	22·0	21·3	34·2

Table 5 *The percentage of registrations for blindness in people aged 65 years and over arranged by cause. Figures for Strathclyde are from Ghatour* et al.[12]

Cause	*Leicestershire*			*Strathclyde 1980*
	1965	*1975*	*1985*	
Senile macular degeneration	38	34	47	39
Cataract	33	32	20	13
Glaucoma	10	10	12	17
Diabetic retinopathy	4	9	2	7
Others	15	15	19	24

aged 65 or over. The percentages obtained in a study of the Strathclyde Region of Scotland in 1980[12] are also included in the table and show a similar distribution. However, care must be taken in interpreting these percentages because a rise in the percentage of registrations due to one cause may be the result of a fall in registrations for another cause. A more reliable indication of trends is given by Table 6, which shows, for men and women, the rates of registration for those aged 65 years or over for each of the four main causes of blindness.

Table 6 needs to be interpreted with care where the rates quoted are small. It will be seen, however, that registrations for both senile macular degeneration and glaucoma rose steadily over the study period. The rise in registrations due to senile macular degeneration is highly significant (p=0·005), while on a much smaller number of cases the rise in registration due to glaucoma does not reach conventional significance levels (p=0·11). The rates of blind registration for cataract and diabetic retinopathy both peaked in 1975, and the difference between the registrations rates of men and women due to cataract was very marked (p=0·0001).

Table 6 *Blindness and partial sight registration of those aged 65 years and over by sex, year, and cause. Rates per 100 000 population*

		SMD	*Cat*	*Glau*	*DR*	*Other*	*Total*
Blindness							
Male	1965	77	50	9	3	21	160
	1975	61	54	12	9	35	171
	1985	95	17	29	8	29	178
Female	1965	68	68	24	9	36	205
	1975	88	85	31	26	39	269
	1985	119	67	29	1	54	271
Total	1965	71	61	18	7	30	187
	1975	77	73	23	20	37	230
	1985	110	47	29	4	44	233
Partial sight							
Male	1965	15	27	12	0	15	68
	1975	31	19	19	0	16	85
	1985	58	12	27	10	41	108
Female	1965	24	51	6	6	9	96
	1975	32	31	23	6	20	93
	1985	85	42	22	4	32	185
Total	1965	21	41	8	3	12	85
	1975	32	26	21	4	19	103
	1985	74	30	24	6	36	170

SMD=senile macular degeneration Cat=cataract Glau=glaucoma DR=diabetic retinopathy.

Since only 15% of those registered in the three years of the study were aged under 65 years, the number of cases is too small to be broken down in a meaningful way. However, if one combines the data for blindness and partial sight across the three years of the study, the main causes of registration in those aged under 65 years were congenital abnormalities (13·5%), glaucoma (13%), optic atrophy (13%), and diabetic retinopathy (9·5%).

Discussion

The age adjusted rates of blind registration given in Table 2 for 1965 are very similar to those quoted by Goldstein[13] as part of an analysis of data collected in 1968 from the whole of England and Wales. In that paper the national overall rate for blindness for 1968 is 26·7 new registrations per 100 000 population. This figure is very close to the 1965 Leicestershire rate of 26·4. It would appear therefore that the Leicestershire data should provide a reasonable indication of national rates and trends.

Although the number of new registrations for blindness in Leicestershire increased by 61% between 1965 and 1985, the largest part of this increase is attributable to changes in the age structure of the population. The same cannot be said of new registrations for partial sight. Here the 146% increase between 1965 and 1985 is far more than would have been expected from the increasing number of elderly people. Indeed, as Table 4 shows, the rate of new registration for partial sight nearly doubled between 1965 and 1985 in those aged 75 and over. This increase probably reflects both a change in registration practice and an increase in public awareness leading to higher demand for treatment or registration.

There are a number of national and local factors that explain the relatively high age and sex adjusted blindness registration rates in 1975 as compared with 1965 and the small reduction between 1975 and 1985. The 1970s were a time of great advance in the treatment of eye disease, with improvements in the ophthalmological care that could be offered to people with such major blinding diseases as senile macular degeneration, diabetic retinopathy, and glaucoma. These improvements meant that more people came forward for treatment and consequently that more blind people were seen and could be registered. Local factors acted to exaggerate this effect During the 1970s Leicestershire's ophthalmic services were upgraded and there was a large increase in the number of ophthalmic consultants in the county. These local factors meant that Leicestershire had a higher adjusted rate of new registrations for blindness in 1975 despite industrial action during that year that might have been expected to decrease the rate. It is likely therefore that the rates for 1965 are low owing to under-registration, and it is to be hoped that the small drop between 1975 and 1985 reflects the improvements in care.

Sorsby[5] noted a higher rate of registration in men as opposed to women in those aged under 50 years but a higher rate among women in the over 50s. A single county does not really give sufficient data to comment on the former claim, but the Leicestershire data do support the view that even after age is allowed for the registration rate for blindness is higher among elderly women. This sex difference is not observed in the registration for partial sight. The excess registration rate in elderly women is particularly evident in the case of registrations for cataract. This finding is in agreement with a number of epidemiological surveys of cataract that have found an excess prevalence of cataract among women.[14]

The importance of senile macular degeneration as a cause of registration for both blindness and partial sight is very marked. Not only is it consistently the major cause of registration but the registration rates in the elderly have been increasing dramatically over the 20-year period covered by the study, with the largest rise occurring between 1975 and 1985.

Despite improvements in treatment, registrations for both blindness and partial sight due to glaucoma have risen steadily over the time of the study. The rise in registrations for blindness is in itself not significant, but when it is viewed together with the figures for partial sight a genuine increase does seem to be present. An explanation for the apparent contradiction between a rising registration rate and improving care may be found in the aging of the population Glaucoma is a progressive disease, and even with good control it may lead to a gradual loss of vision.[15] Although the rates in Table 6 are adjusted for the number of people aged 65 and over, this group has itself changed in character over the time of the study. In 1965, 36% of this age group were aged 75 years or more, but by 1985 this figure had risen to 43%.[7,8,10] There are now a greater proportion of people living into their 80s and 90s. As a result of this continuing change in the age structure in the elderly population the registration rates in those aged 65 and over for such progressive diseases as glaucoma may be expected to continue to increase.

The numbers of cases of blindness due to diabetic retinopathy were small and must therefore be interpreted with care. However, Table 6 also shows how, for the elderly, a large proportion of the increase in blind registration between 1965 and 1975 was due to diabetic retinopathy. For the reasons given above it is likely that a large part of this rise is due to under-registration in 1965. For diabetic retinopathy the fall in blind registration rates between 1975 and 1985 was just as dramatic as the previous rise. The reasons for the subsequent fall can be found in the increasing use of laser treatment and better local care resulting from the introduction of a specialist retinal service in the late 1970s. Ironically the introduction of the retinal service is probably partly responsible for the gradually increasing rate of partial sight registration due to diabetic retinopathy. Better contact with patients has meant that they are more likely to become registered. As with glaucoma, the other factor that acts to increase the rate of partial sight registration is the aging of the population.

The national blindness registration system was set up to identify people in need of state help, and consequently registration is compulsory only if a person wishes to claim extra state benefits. For this reason the register will tend to underestimate the actual levels of blindness in a community. It is difficult to estimate the extent of underestimation because differences in local practice lead to wide variations in the extent of registration.[16] One study in Canterbury has suggested that the register may underestimate the extent of blindness by as much as 33% of potential cases and the extent of partial sight by 17%.[17] A large study in Wales found that the blind register had omitted some 29% of those who were eligible for registration.[18]

Because of the wide regional variations the best indication of the completeness of the Leicestershire register comes from a recent study by Gibson *et al.*[19] They used a community study of those aged over 75 years in a single Leicestershire town to test the completeness of the local register and found that the blind register contained 87% of those who were eligible under WHO criteria[20] and that the partial sight register contained 50% of those who were eligible. In both cases they found that the registers had specificities of over 99%, so that very few people were being registered who were not blind or partially sighted. It seems that local practice in Leicestershire is sufficiently good to allow one to assume that the blind register gives a good indication of the extent of actual blindness in the community. The partial sight register is probably much less complete, and, although registration is of interest in its own right, care must be taken in interpreting its wider epidemiological significance.

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Dehydrational crises: a major risk factor in blinding cataract

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SUMMARY An earlier case control investigation has indicated a strong relationship between dehydrational crises and risk of presenile cataract. A second methodologically distinct case control study of risk factors in cataract has been carried out in a population very different in terms of environmental and sociocultural characteristics from the population investigated in the earlier study in Central India. The results strongly confirm the findings from the first study and indicate that an estimated 38% of blinding cataract may be attributable to repeated dehydrational crises resulting from severe life threatening diarrhoeal disease and/or heatstroke. The risk of blinding cataract was strongly related to level of exposure to dehydrational crises in a consistent and dose dependent manner, thus indicating a causal association. The findings are discussed in relation to possible sources of bias in the study, confounding in the data, and the steps that were taken to minimise their undesirable effects.

A matched-pair case-control study conducted in Raipur, Central India, has shown for the first time that the risk of presenile cataract may be substantially increased by exposure to severe life threatening diarrhoeal disease and to heatstroke.[1] The data suggest that approximately 40% of the cataracts in the population studied might be attributed to crises of severe dehydration. If these findings could be substantiated and generalised to other populations in India and elsewhere, then a major cause of the biggest blinding disease worldwide would have been discovered. To this end a methodologically distinct case control study was conducted in Titlagarh, Orissa, in a population that was markedly different from that in Raipur in terms of ethnic, socioeconomic, cultural, and environmental factors.

Material and methods

The study was carried out in a small eye unit in a long established general practice in the town of Titlagarh in Orissa. The eye unit serves a good mixture of urban and rural populations from the town and its surrounding villages, providing a high-quality primary eye care service and referral for intraocular surgery, free of charge.

During a 24-month period all patients aged 30 to 69 who attended the eye unit and who could be categorised as cases (cataract) or controls, according to a predefined set of diagnostic criteria, were included in the study. There was no deliberate selection of controls by matching.

All the systematic examinations and interviews were conducted by one specially trained ophthalmic assistant working under the supervision of the senior physician in charge of the practice, with regular and frequent quality control checks made by one or other of the ophthalmologists in charge of the study. Throughout the period of field work the ophthalmic assistant was unaware of the definition of cases and controls.

EXAMINATIONS

All patients aged 30 to 69 attending the eye unit during the study period were systematically tested and examined to assess visual acuity and central lens opacities. The red reflex of each eye was visualised through the undilated pupil with a direct ophthalmoscope set at +2·00 dioptres and held at approximately 1/3 m from the patient's eye. Central lens opacities that partially (or wholly) obscured the red reflex were identified and graded as 0, 1, 2a, 2b, or 3 according to the area of opacity in relation to area of clear red reflex. Grade 3 indicated complete obscuration of the

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red reflex by the lens opacity. In addition aphakia was recorded as grade 4, and grade 5 indicated inadequate view or unable to assess the red reflex, usually due to corneal opacity. The standard method of examination and grading of central lens opacities has been assessed in the field in an observer variation study and is described in more detail elsewhere.[2] Further detailed eye examinations including refraction and funduscopy were carried out according to the diagnostic routine of the clinic.

The general examinations included measurement of the patient's height and weight as an index of nutritional status and screening for diabetes.

DEFINING THE CASES AND THE CONTROLS

The predefined criteria for diagnosis of the 'case' (unknown to the examiner and interviewer) were 'sufficiently advanced central lens opacity (grade 2A or worse)[2] that impaired the vision to less than 6/18'. All the remaining patients were taken as unselected controls.

INTERVIEW

The interviews took place in a specially prepared area in the clinic, away from the busy routine of the practice. The interview procedure, used in the study to ascertain exposure to the possible risk factors under investigation, had been previously tested and standardised in extensive pilot studies covering more than 600 interviews in rural and urban settings. In particular, the key questions, which concerned past experience of severe life threatening diarrhoeal disease, were tested and refined (with due regard to the local culture) so that they focused on episodes of illness that should have been memorable. Fig. 1 shows the sequence and the English translation of the questions that were asked systematically and in a standard fashion in all the study subjects regardless of their cataract status.

To avoid possible recall bias the diarrhoea questions were hidden among many other interview topics which included smoking habits, tobacco chewing, access to clean water, occupation, etc. Past

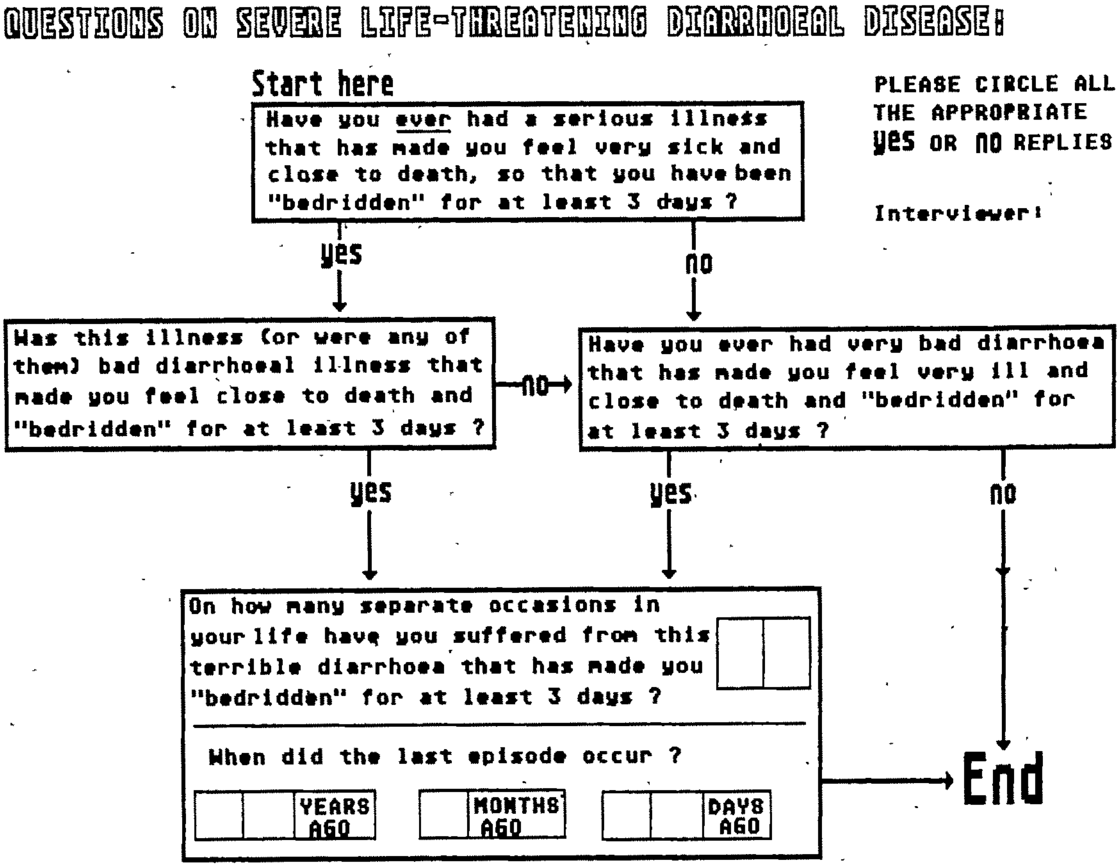
QUESTIONS ON SEVERE LIFE-THREATENING DIARRHOEAL DISEASE:
Start here
Have you ever had a serious illness that has made you feel very sick and close to death, so that you have been "bedridden" for at least 3 days ?
PLEASE CIRCLE ALL THE APPROPRIATE yes OR no REPLIES
Interviewer:
yes
no
Has this illness (or were any of them) bad diarrhoeal illness that made you feel close to death and "bedridden" for at least 3 days ?
no
Have you ever had very bad diarrhoea that has made you feel very ill and close to death and "bedridden" for at least 3 days ?
yes
yes
no
On how many separate occasions in your life have you suffered from this terrible diarrhoea that has made you "bedridden" for at least 3 days ?
When did the last episode occur ?
YEARS AGO
MONTHS AGO
DAYS AGO
End

Fig. 1 *Content and flow of questions to ascertain past exposure to severe cholera-like diarrhoeal disease. A version in local dialect was used in this field.*

Table 1 *Information ascertained systematically from each patient*

Age, sex, place of birth, place of residence
Occupation Farmer, business, landless labourer, professional, etc.
Place of work· mostly outdoors, mostly indoors, mixed
Social caste: low, middle, high
Economic status· an index based on income, family size, ownership, etc
Main source of water pond, river, unprotected well, well, pump, etc.
Number of years each source used
Cigarette smoking number per day and years smoked
Tobbaco chewing. years chewed
History of severe life threatening diarrhoeal disease see Fig 1
History of heatstroke. number of episodes with year of occurrence

Weight and height· standardised measurements
Screening for diabetes: including urine test
Assessment of visual acuity
Assessment of cataract central lens opacities
Assessment of the principal cause(s) of visual impairment

Routine diagnostic procedures of the eye unit

exposure to heatstroke was similarly ascertained through use of the local term that referred to a uniformly serious condition, a 'stroke', expected to be a memorable event and accompanied by dehydration A list of all the interview topics is included in Table 1

ANALYSIS OF DATA

The data were recorded on predesigned forms which were transferred into a computer database specially designed for management of case control data.

Statistical methods of analysis comprised a rational sequence and mixture of the classical methods[1-6] and of more recently developed multivariate log-linear modelling techniques.[7] Preliminary cross-tabulations were carried out to identify the main factors and their covariates that were strongly associated with the case control status (cataract). The data were then stratified accordingly into multidimensional cross-tabulations so that comparisons of cases and controls in respect of exposure to a particular factor could be done within groups that were matched for other key risk factors that might be confounders.

Multivariate log-linear modelling was applied to the stratified data to explore further the interrelationships between exposure factors and cataract. However, the main objectives in log-linear modelling were to confirm the presence or absence of higher-order interactions that might indicate effect modification (that is, heterogeneity of the relative risks in subgroups of the population as defined by the stratification). Summary estimates of the relative risks across the strata were then computed only when justified by the absence of evidence to indicate such heterogeneity.

Associations between cataract and exposure to one or combination of risk factors were quantified by computing the crude and the standardised or summary odds ratios that were so far as possible free of confounding, according to methods proposed by Mantel, Haenszel, and Miettinen.[3-5] Mantel's extension of the Mantel-Haenszel procedure was used to test the statistical significance of trends in increasing risk of cataract with rising levels of exposure. The computed odds ratios are regarded as estimates of the relative risk and are referred to as such in the paper

All the various exposure levels considered for each possible risk factor were defined before any data analysis and were not altered at any stage during the data analysis. For example, exposure to dehydrational crises was graded into 4 levels of hypothesised increasing exposure, exactly as for the previous study in Raipur. No other rearrangement or regrading was explored in the analysis.

Information on all the study factors was used to evaluate the relationship between cataract and dehydrational crises. However, only the results that concern the association between cataract and dehydrational crises are reported in this paper. The findings relating to the other risk factors and cataract will be reported in separate publications.

Results

A total of 1644 consecutive patients aged 30–69 were examined and interviewed. Of these, 1364 persons were aged 30–59 and comprise the sample for this report.

Examinations identified 434 cases (persons with central lens opacity reducing the vision to less than 6/18) and 930 controls. The age and sex distribution of the sample is shown in Table 2. Analysis of the results strongly suggests a marked, consistent, and dose dependent association between: (*a*) exposure to dehydrational crises (dehydration), as ascertained by history of remembered episodes of severe life threatening diarrhoeal disease and/or heatstroke;

Table 2 *Age and sex distribution of 1364 patients in the study*

	30–34	*35–39*	*40–44*	*45–49*	*50–54*	*55–59*	*Totals*
Males	56	69	90	253	206	207	881
Column %	75 7	67 6	53 3	62 3	61 7	74 2	64 6
Row %	6·4	7 8	10 2	28 7	23 4	23·5	100 0
Females	18	33	79	153	128	72	483
Column %	24 3	32 4	46 7	37 7	38 3	25 8	35·4
Row %	3 7	6 8	16·4	31 7	26·5	14·9	100 0
Totals	74	102	169	406	334	279	1364
Total %	5 4	7 5	12 4	29 8	24·5	20 5	100 0

Table 3 *Association of blinding cataract with any exposure to severe life threatening diarrhoeal disease (one or more remembered episodes). The data are summarised by six age strata only*

Age groups		*Not exposed*	*Exposed*	*Totals*	*Relative risk*	χ^2	*p Value*
30–34	Controls	59	11	70			
	Cases	2	2	4	5·36	3·03	0·082
35–39	Controls	69	24	93			
	Cases	4	5	9	3·59	3·53	0·06
40–44	Controls	103	29	132			
	Cases	13	24	37	6·56	24·5	<0·001
45–49	Controls	190	95	285			
	Cases	60	61	121	2·03	10·45	0·0012
50–54	Controls	130	76	206			
	Cases	44	84	128	3·27	26·04	<0·001
55–59	Controls	84	60	144			
	Cases	57	78	135	1·92	7·21	0·0072
All	Controls	635	295	930			
ages	Cases	180	254	434	3·04	88·34	<0·001
Totals		815	549	1364			

Summary (unconfounded) relative risk = 3·02
95% confidence limits = 2·3 and 4 •
Summary χ^2 (Mantel/Haenszel) = 63 (p value <0·001)

and (*b*) the risk of visually disabling central lens opacities (cataract).

For exposure to one or more episodes of severe diarrhoeal disease the summary (unconfounded) relative risk estimate was 3·02 with 95% confidence limits of 2·3 and 3·97 (Table 3). This, like the other reported summary estimates, is as far as possible free from confounding by age, sex, and other exposure factors studied. The finding suggests that the actual risk of blinding cataract is on average 3 times higher in those exposed to severe diarrhoeal disease than in those not exposed, in the age range studied. The likelihood is 95% that the actual relative risk is not less than about 2·3 and not more than about 4. Log-linear modelling and a classical test of homogeneity indicated that the relative risks were uniform in the various age/sex strata.

There was a significant trend of increasing relative risks with rising level of exposure to severe diarrhoeal disease. The trend was consistent in the various age/sex strata. In the youngest age group (30–39) the relative risk estimates for exposure to only one episode of severe diarrhoeal disease was about 2·3. For exposure to 2 or more episodes the relative risk was 12. These suggest that the risk of blinding cataract may be increased 2-fold in those with the lower level of exposure and as much as 12-fold in the higher exposure group, all compared with the not exposed. As expected, the trends were not identical in all the strata in the data. However, log-linear modelling indicated that the variations in trend between the strata were small and did not indicate real differences. This lack of convincing evidence for heterogeneity justified computation of overall summary relative risks for each level of exposure to arrive at a summary trend. The summary trends and some of the stratum specific trends are shown in Table 4.

There were consistent and strong 'dose dependent' relationships between risk of cataract and four levels of increasing exposure to dehydrational crises (exposure to diarrhoea and/or heatstroke). The trend was most marked in the youngest age group. However, log-linear modelling again indicated homogeneity across the strata. The summary and some of the age-specific relative risks are shown in Table 5. The trends are displayed in Fig. 2.

Table 4 *Trends of increasing risk of blinding cataract with rising levels of exposure to severe life threatening diarrhoeal disease (0, 1, or 2+ episodes). The data are summarised by six age strata only. Relative risk (RR) estimates are shown for each 10-year age class*

Age groups		*Levels of exposure to severe diarrhoeal disease*				*Trend* χ^2	*p Value*
		0	*1*	*2+*	*Totals*		
30–34	Controls	59	9	2	70		
	Cases	2	2	0	4		
35–39	Controls	69	19	5	93		
	Cases	4	1	4	9		
Relative risks		1	2·3	12·2		10·7	0·001
40–44	Controls	103	20	9	132		
	Cases	13	17	7	37		
45–49	Controls	190	68	27	285		
	Cases	60	36	25	121		
Relative risks		1	2·4	3·6		29·2	<0·001
50–54	Controls	130	53	23	206		
	Cases	44	42	42	128		
55–59	Controls	84	46	14	144		
	Cases	57	45	33	135		
Relative risks		1	1·9	4·3		41·6	<0·001
Total sample					1364		
Summary RRs (Mantel/Haenszel)		1	2	4·1		78·5	<0·001

Log-linear modelling indicated homogeneity of the trend in RRs across all the age strata

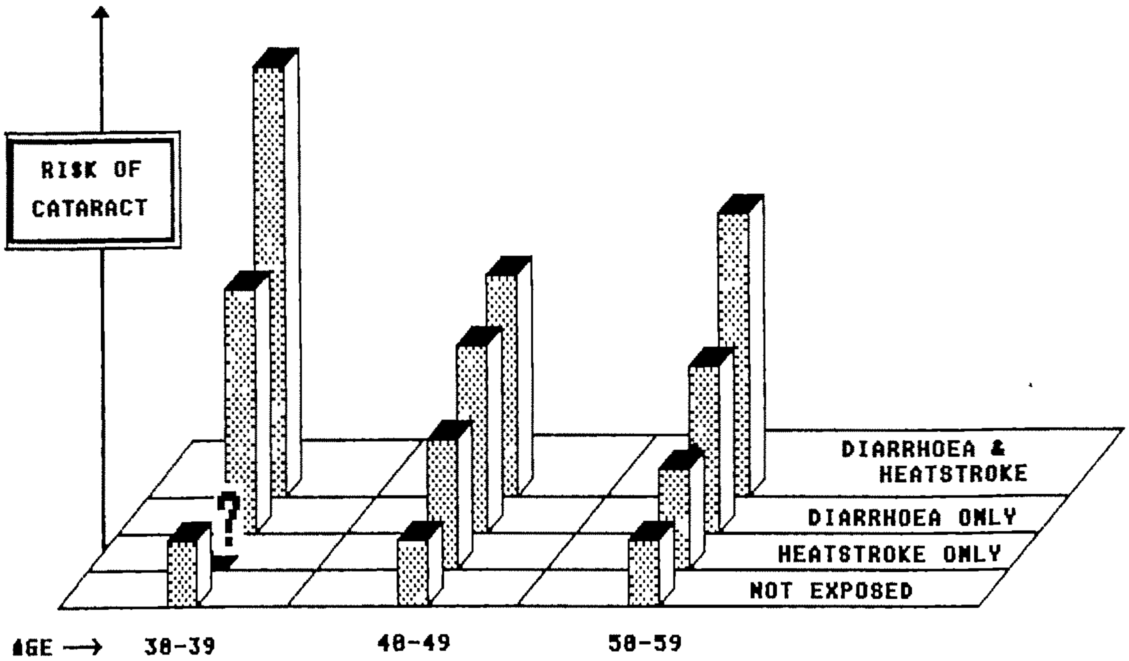

Fig. 2 *Trends of increasing risk of blinding cataract with rising levels of exposure to dehydrational crises The relative risks should not be compared between the age groups, as the baseline risk in each age group is set to 1.*

Table 5 *Trends of increasing risk of blinding cataract with rising levels of exposure to 'dehydrational crises'. Relative risk (RR) estimates are shown for each 10-year age class*

Age groups		*Levels of exposure to dehydrational crises**					*p Value*
		0	*1*	*2*	*3*	*Totals*	
30–34	Controls	54	5	10	1	70	
	Cases	2	0	2	0	4	
35–39	Controls	65	4	22	2	93	
	Cases	4	0	4	1	9	
Relative risks		1	77	3 7	6·6		0·008
40–44	Controls	99	4	28	1	132	
	Cases	11	2	21	3	37	
45–49	Controls	179	11	91	4	285	
	Cases	55	5	60	1	121	
Relative risks		1	2	2 9	3·4		<0·001
50–54	Controls	121	9	73	3	206	
	Cases	41	3	82	2	128	
55–59	Controls	83	1	59	1	144	
	Cases	53	4	72	6	135	
Relative risks		1	1 5	2·5	4·3		<0·001
Total sample						1364	
Summary RRs (Mantel/Haenszel)		1	1·7	2 7	4		<0 001

Log-linear modelling indicated homogeneity of the trend in RRs across the age strata

*0=no exposure.
1=exposed to heatstroke only (one or more episodes).
2=exposed to severe diarrhoeal disease only (one or more episodes).
3=exposed to both heatstroke and severe diarrhoea.

The overall unconfounded population attributable risk (PAR) for exposure to dehydrational crises was estimated to be about 37% for each of the age groups 30–39 and 40–49, and about 39% for the oldest age group (Table 6). The summary estimate for the population was 38%. The findings suggest that about 38% of the visually disabling cataract in the population may be attributed to dehydrational crises.

Discussion

The findings support the hypothesis of a causal association between repeated episodes of dehydrational crises and blinding cataract. They also suggest that a substantial proportion of visually disabling cataract is avoidable through prevention or control of severe acute dehydration. However, in this as in any

Table 6 *Population attributable risks (PARs). Proportion of the blinding cataract that may be attributable to 'dehydrational crises'. The unconfounded estimates of PAR are shown for each 10-year age class and also as a summary measure for the whole data set*

Age groups	*PAR*	*95% Confidence limits*
30–39	36·8%	
40–49	37 3%	
50–59	38·7%	
Summary PAR	38%	26% and 49%

other case control study, it is possible that the reported relative risks were grossly over- or underestimated because of bias arising from the study and/or confounding. It is therefore essential to review the main potential sources of bias that might have arisen and to discuss what was done to minimise their undesirable effects.

Possible bias from selection of cases and controls. The study was designed to estimate the risk of visually disabling cataract in patients exposed to dehydrational crises compared with those not exposed. The cases therefore comprised persons with central lens opacities that reduced vision to less than 6/18. The controls were the remaining patients attending the clinic. Some of the controls also had lens opacities, but these were not advanced enough or sufficiently central in location to cause serious visual impairment. It would have been inappropriate to exclude such controls from the analysis. Had we done so the estimates of relative risk would be considerably higher, but spuriously so. Furthermore, such exclusions would make it very difficult to interpret the population attributable risks in a useful way.

Possible bias from ascertainment of past exposure. It may be argued that in spite of the great emphasis on the severe life threatening nature of the illness on which the interview focused, many subjects could have been incorrectly classified as exposed (or not exposed) because of poor recollection of the past episodes. This would imply that the method of ascertaining past exposure to dehydrational crises had poor sensitivity and poor specificity in detecting presence or absence of exposure. If this were true, the reported relative risks can only be underestimates. Poor sensitivity and/or poor specificity would tend to mask some component of the relative risks, provided the ability of the interview in detecting past exposure was equally poor (that is, unbiased) in both cases and controls. An important aspect of the repeated quality control checks that were made throughout the study was to ensure that all the subjects regardless of their case control status continued to be interviewed in the same manner by the same interviewer using the standardised method. We are therefore reasonably certain that bias from this potential source was minimal, if any. We are equally certain that our estimates of relative risk are not exaggerated and are best regarded as minima.

Persons were considered exposed only when the episode of exposure preceded the cataract induced visual disability by three months or more. The consistent and marked trend of increasing risk with rising levels of exposure would be difficult to explain in terms other than that of a causal association between cataract and dehydrational crises. The hypothesis of causal association is strengthened by the similarity of the findings to those of the previous study in Raipur (almost identical population attributable risk estimates), particularly in view of the substantial differences in the methods of the two studies and in the environmental and sociocultural characteristics of the two populations studied.

In order to be able to generalise the hypothesis to other populations we strongly recommend that similar investigations should be done (preferably also by other groups of workers) in other locations. However, unless the past exposure to severe diarrhoeal disease is ascertained with great care and due emphasis given to the severity of the episodes, it is unlikely that a relationship could be demonstrated.

Our thanks to Dr Hasmuk for his valuable supervision and for making available the eye unit in his practice, and to Mr Lallit for conducting the interviews and examinations with such great care.

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Delayed microhyphaema with intraocular lenses: a retrospective study of eight patients

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SUMMARY Eight patients with delayed microhyphaema were identified from a computer data base of 1209 patients who had had cataract extraction with Binkhorst 4-loop intraocular lens insertion. Five cases were recurrent. The cases were examined to try and identify an underlying cause. No single cause was identified, but trauma, hypertension, and oral anticoagulants were found to be associated. Some episodes were asymptomatic. The wide variety of surgical technique and style of lens with which this complication has been reported implies multiple causative factors. The source of the bleeding and its management are discussed.

Delayed intraocular haemorrhage has been described in association with many types of intraocular lens since it was first reported by Ellingson[1] in 1977 as part of the uveitis-glaucoma-hyphaema (UGH) syndrome. Various suggestions have been made concerning aetiology and various approaches have been taken to management. No consensus has emerged.

We began this retrospective study after an initial impression that patients we saw were frequently on oral anticoagulants and moreover were well controlled. All the patients in this study are patients of one consultant (MJR-H). All with one exception, no. 8, have had cataract surgery by an identical technique. Following an intracapsular cataract extraction (ICCE) via a corneal section a Binkhorst 4-loop iris supported lens (BIOL) was inserted and secured with a single 10/0 polypropylene iris suture. Sodium hyaluronate was first used in 1983. A special BIOL follow-up form was filled in when patients attended either for routine follow-up or with acute problems. The results were transferred to a computer, and it is from those data, derived from some 1209 patients, that we identified additional patients. We have identified eight patients who have suffered one or more episodes of non-layering microhyphaema. There were no bilateral cases.

Case reports

CASE 1

Two years after left ICCE+IOL (at age 59 yr) she presented with mild painless blurring of the vision in her left eye. Her vision was 6/12 corrected. On examination there was a fine vertical spindle of red blood cells (RBCs) on the lower half of the corneal endothelium. No other ocular abnormalities were found. The operation notes record a shallow anterior chamber (AC) and some touch between the BIOL and the corneal endothelium at the time of lens insertion. In April 1982 she had had an uncomplicated myocardial infarction. There was no preceding history of trauma nor of drugs associated with coagulation defects. The episode resolved spontaneously and has not recurred. Follow-up time was 5·3 yr.

CASE 2

In December 1985 a previously fit 62-year-old man presented with a three-month history of right visual distortion. He had had a right ICCE+BIOL in 1984, when sodium hyaluronate had been used because of a shallow AC. His vision was still 6/9 but with distortion. There was a corneal RBC spindle but no RBCs or cells in the AC. The intraocular pressure (IOP) was elevated at 27 mmHg, and there was an iris sphincter tear temporally. A small macular haemorrhage was thought to be the cause of the visual distortion. He was found to be hypertensive. Topical treatment included pilocarpine drops 1% to immobilise the pupil. Subsequent difficulty in controlling his blood pressure was associated with a central retinal vein occlusion and vitreous haemorrhage. Although the vitreous cleared over the next 12 weeks, a corneal spindle could still be seen seven and 22 months later. Follow-up time was 3·9 yr.

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CASE 3

In 1976 a fit 40-year-old woman had an uncomplicated right cataract extraction for a congenital cataract. In October 1980 she was hit on the right maxilla and became aware of blurred vision in the right eye 24 hours later. When she was seen four days later her vision was 6/6 in each eye and the only abnormality was an RBC spindle in the right eye. No treatment was given and she was lost to follow-up until May 1985, when she was again hit on the face. Again the only abnormality was an RBC spindle. There have been five or six spontaneous episodes since then, none requiring treatment. The pupil on the right is closely applied to the pillars of the BIOL, with very minimal sphincter atrophy. Follow-up time was 9·5 yr.

CASE 4

Twelve months after an uncomplicated left ICCE+IOL at age 57 years this patient was anticoagulated for rheumatic heart disease and myocardial ischaemia. She had an isolated microhyphaema 20 months later but developed a left traumatic hyphaema after hitting her eye with the handle of a carpet sweeper. This resolved spontaneously, but over the succeeding months she had multiple episodes of blurred vision (at least 26 between March 1979 and May 1981). When she was examined the episodes were characterised by an RBC spindle and occasionally RBCs in the AC. Pilocarpine drops were prescribed. An increase in the frequency of episodes occurred after difficulty in control necessitated an alteration in her warfarin dosage. Her prothrombin time remained within the therapeutic range throughout. There was some response to a decrease in warfarin, but when last seen in 1983 she was still subject to transient blurring in that eye. No areas of sphincter damage were seen, but the pupil was noted to be very mobile. She died in 1984. Follow-up time was 10·5 yr.

CASE 5

Nineteen months after an uncomplicated right ICCE+BIOL at age 66 years she suffered an asymptomatic microhyphaema. A typical RBC spindle was seen. The only other feature was an IOP at 25 mmHg. Treatment with pilocarpine drops 1% was begun. There was no sphincter damage. A second asymptomatic episode occurred 14 months later. She is still being followed up. Follow-up time was 2·6 yr.

CASE 6

Seventy two months after an uncomplicated right ICCE+BIOL at age 62 years this woman attended the casualty department with a spontaneous microhyphaema. She was stable on anticoagulants for rheumatic heart disease. The IOP on the right was slightly higher than on the left (20 to 15 mmHg). The BIOL was secure, with posterior synechiae to each pillar, but with extensive iris transillumination in adjacent areas. There was no history of trauma or of factors that might have altered her warfarin control. Her prothrombin time (PT) was within the therapeutic range (2·0–4·0), but her warfarin dose was temporarily reduced to achieve a ratio of under 2·0. Repeated examinations failed to reveal any site of bleeding. No specific treatment was given. Follow up time was 7 yr.

CASE 7

At the age of 44 years she had a right ICCE+BIOL with vitreous loss. She achieved 6/5 vision. Eight years later she complained of occasional mistiness in her right eye. During these episodes an RBC spindle was the only abnormality. There was no history of trauma or drug ingestion. No treatment was given, and the episode resolved. She has since moved out of the area and has been lost to follow-up. Follow-up time was 11·5 yr.

CASE 8

At the age of 37, 24 years after blunt trauma (with hyphaema, sphincter damage, lens subluxation, and vitreous prolapse into the AC) this man required right cataract extraction. After delivery of the lens with a loop, an anterior vitrectomy and sphincter repair, a BIOL was inserted without complication. He achieved 6/9 vision. Postoperatively his pupil was pentagonal, and, perhaps significantly, no posterior synechiae formed to the BIOL pillars. In August 1984 he presented with pain and decreased vision in this eye. There was a diffuse hyphaema and blood in the anterior vitreous. The IOP was normal. The blood was reabsorbed on bed rest. Over the next 12 months he had recurrent hyphaemas of varying severity. In 1985 the BIOL was rotated through 45° in the coronal plane, and an additional iris suture inserted to prevent IOL rotation. For a while he continued to have microhyphaemas, but from March 1987 he had been symptom-free since having atropine drops 1% on alternate days. Repeated examination failed to reveal an obvious source of bleeding, but marked areas of iris transillumination existed adjacent to each pillar and round the peripheral iridotomies (PIs). Clotting studies gave normal results except for a bleeding time at the upper limit of normal (IVY method). This is not thought to be of clinical significance. Follow-up time was 6 yr.

Cases 1, 3, 5, and 7 have also had cataract surgery in the fellow eye.

Discussion

ANTICOAGULATION

In our study only two patients (nos. 4 and 6) proved to be on anticoagulants. They were both well controlled on warfarin for rheumatic heart disease. Case 6 has had a single episode at a time when her prothrombin time ratio (2·8) was well within the therapeutic range. We failed to identify anything that might have altered her response to the drug.[23] It is difficult to be certain if the resolution of the episode that occurred when the dose was reduced was more than chance coincidence. Case 4 had at least one episode prior to the ocular trauma. Although she was under the supervision of a local anticoagulant clinic, control was variable and associated with an increase in the frequency of episodes. A third patient, no. 8, was found to have a bleeding time just outside the normal range, but this is of doubtful clinical significance. All three were among those most severely affected, either in amount of bleeding or in the number of episodes. Only one other patient, no. 3, has had multiple bleeds.

The increased risk of spontaneous hyphaema in patients on oral anticoagulants has been discussed.[4] Schiff[5] reported five cases, all with iris supported lenses, who developed spontaneous hyphaemas after starting warfarin. However, no details of control were given, and four bled within the first few weeks of beginning the drug. It is possible that they were not yet stable.

TRAUMA

Postoperative trauma seems to have been a precipitating event in one, case 3, and implicated in the onset of recurrent episodes in one other, no. 4. Three other patients, nos. 1, 2, and 7, were recorded as having an intraoperative event at the time of BIOL insertion. We wonder whether this may have resulted in minor and overlooked areas of iris trauma and that such areas might be susceptible to bleeding under the influence of later events. Patient 8 suffered severe preoperative trauma, including iris sphincter damage. Gonioscopy failed to reveal abnormal angle vessels. Four patients in our series have had multiple bleeding episodes. Three, nos 3, 4, and 8, had ocular trauma of a degree that warranted attendance for examination. One, case 4, was also on warfarin.

CARDIOVASCULAR DISEASE

The onset of haemorrhage in case 2 led to the diagnosis of hypertension. Hypertension can also rarely present with epistaxis. Subsequent difficulty in controlling his blood pressure is likely to have been a factor in his central retinal vein occlusion. The endothelial spindle persisted much longer than the vitreous haemorrhage and may indicate recurrent anterior segment bleeds. Patients with cataract, because of their age, are quite likely to have coexistent cardiovascular disease. Case 1 had an uncomplicated myocardial infarction prior to the onset of his visual symptoms. It is interesting to speculate whether arteriosclerosis has a direct role or whether it simply makes the patient more likely to develop hypertension or to need anticoagulation. A quarter of the patients reported on by Johnson *et al.*,[6] with iris transillumination defects and microhyphaemas after insertion of sulcus fixated posterior chamber IOLs, had had surgery for cardiovascular disease.

We could not identify any factors for patient 5.

We noted with interest that the average age of the patients in the series was considerably lower (53·37 yr) than the averages of the groups from which they came—68·35 (NHS patients) and 67·91 (private patients). The series does contain one patient aged 40 yr who required cataract surgery following trauma and one aged 44 yr with congenital cataracts, but, even if they are excluded, the average is only 58·4 yr. Since episodes may be asymptomatic, we may not have identified all affected patients, and thus the real average may be different.

SOURCE OF BLEEDING

The identification of the source of bleeding in such spontaneous microhyphaemas is important if a rational approach to prevention and management is to be adopted. In 1973 Swan[7] reported three cases of sudden transient blurring of vision in aphakic eyes with gonioscopic evidence of vascularisation of the limbal wound and fresh haemorrhage. They were treated with focal laser coagulation or surgical excision of the vascularised area. From a survey of 58 aphakic eyes examined 5–10 years after surgery Watzke[8] found 12% with episcleral vessels on the inner aspect of the wound and that almost half showed evidence of mild intraocular haemorrhage. He believed that, while these vessels were a common source of such haemorrhage, treatment was usually unnecessary. Defective wound healing, coarse silk and gut suture, ingrowth of episcleral vessels, and trauma have all been implicated as causes of wound vascularisation.[7] All our patients had incisions in clear cornea, and while superficial vascularisation of these incisions is not uncommon we have not observed deeper vessels of the type that would be required. The section in our patients would also be a very visible source of even a minor bleed. Detailed gonioscopy was performed on all but patient 4 without evidence of abnormal vessels being found.

When an iris fixated or ciliary sulcus fixated lens is used, the posterior surface of the iris becomes another possible source. In a detailed study by Nicholson[9] of one patient with a Binkhorst 4-loop lens who suffered multiple anterior chamber bleeds angiography showed an abnormal iris vascular pattern on the anterior iris surface. Radial vessels were displaced adjacent to the superior pillars, and there was an area of leakage adjacent to one. He blamed these on recurrent iris chafing by the lens. Schiff also observed leakage on iris angiography adjacent to areas of sphincter erosion.[5] Areas of iris transillumination over the loops of angulated sulcus fixated IOLs are well recognised but said to be uncommon. Estimates vary from 5 to 15%.[6 8] Similar chafing defects have been observed corresponding to the edges of the optic in a uniplanar posterior chamber lens. Some of these patients also show transient microscopic hyphaemas characterised by an RBC spindle and clear aqueous.[6 10] In at least one patient active streaming of RBCs from the posterior iris surface was seen.[6] Small volumes of blood would be carried forward in the aqueous circulation currents and, by analogy with pigment in the pigment dispersion syndrome, be deposited as an endothelial spindle. Areas of sphincter damage were seen in four of our patients. Preoperative, operative, or postoperative trauma might produce small areas of iris damage vulnerable to secondary factors. These include repeated trauma (including a very mobile pupil) and hypertension. The very frequent bleeds seen in one patient on warfarin suggest that small breaches in the vessel walls may be occurring often. Only in the presence of defective coagulation are these made manifest.

COMPLICATIONS

The most common complaint in our series is of blurred vision, though the episodes can also be asymptomatic. In most patients there was no permanent decrease in visual acuity. A more prolonged decrease in vision occurs if the anterior hyaloid face is broken and blood enters the vitreous. If the bleeding is severe enough, a ghost cell glaucoma may been found.[11] The IOP may also be elevated by the crowding of fresh RBCs in the angle. We found no evidence of the creeping angle closure noted by Swan.[7]

While the diagnosis may be obvious, in some cases a small spindle may be easily overlooked. More than one patient has been investigated for amaurosis fugax, and at least one has had carotid angiography—a procedure not without its own risks.[6 10 12]

MANAGEMENT

Various approaches have been tried. Miotics and mydriatics are used to immobilise the pupil and thus minimise lens-iris chafing.[10] Pilocarpine drops were used in three of our patients. They have the additional benefit of being an ocular hypotensive agent. Atropine drops were also used to good effect in one. Additional McCannel iris sutures can also reduce IOL movement. Berger[13] believes that nocturnal trauma is an important factor and therefore recommends the use of a plastic eye shield at night. The management of systemic factors such as hypertension, and anticoagulant control, are theoretically important. A logical approach for those who do require active intervention is laser ablation of areas of vascular leakage identified by iris angiography (on the assumption that these are responsible).

It is important to remember that not all patients will require treatment.

CONCLUSION

A spontaneous hyphaema, either on its own or as part of the UGH syndrome, is not now thought of as just a complication of poorly finished rigid AC lenses. It has also been seen in association with flexible AC lenses, iris supported lenses, and sulcus fixated posterior chamber lenses. The real incidence of this uncommon complication is difficult to establish. It is likely that patients who suffer an isolated, transient blurring of vision may not attend for examination. Some clinically detectable episodes seem to be asymptomatic. Even patients who do attend may be misdiagnosed if the only evidence is an RBC spindle which is overlooked. While we have looked at those patients known to us, it would seem unwise to extrapolate a true incidence from these figures. Moreover different surgeons using different techniques and lens styles are likely to find different levels of incidence.

The evidence of iris angiography and the clinical impression from the observed endothelial spindle formation is in favour of a posterior iris source for iris supported and sulcus fixated IOLs, the likely sites being areas of pseudophakos-iris chafing. The aetiology is likely to be multifactorial, comprising local, systemic, and temporal factors. This study provides three factors that need to be considered: trauma (preoperative, operative, and postoperative); cardiovascular disease, particularly poorly controlled hypertension; and oral antiocoagulants. Trauma seems to be particularly associated with multiple episodes of bleeding Not all patients will require active treatment. In those who do the most logical approach seems to be ablative laser applications to areas identified by iris angiography.

The pseudophakic eye is a system in delicate balance. Histopathological evidence emphasises the inflammatory response to all types of intraocular lenses.[14 15] These responses seem to be less with lenses implanted 'in the bag'.[15] Delayed recurrent microhyphaema is another, probably under-recognised, reason for adopting this technique.

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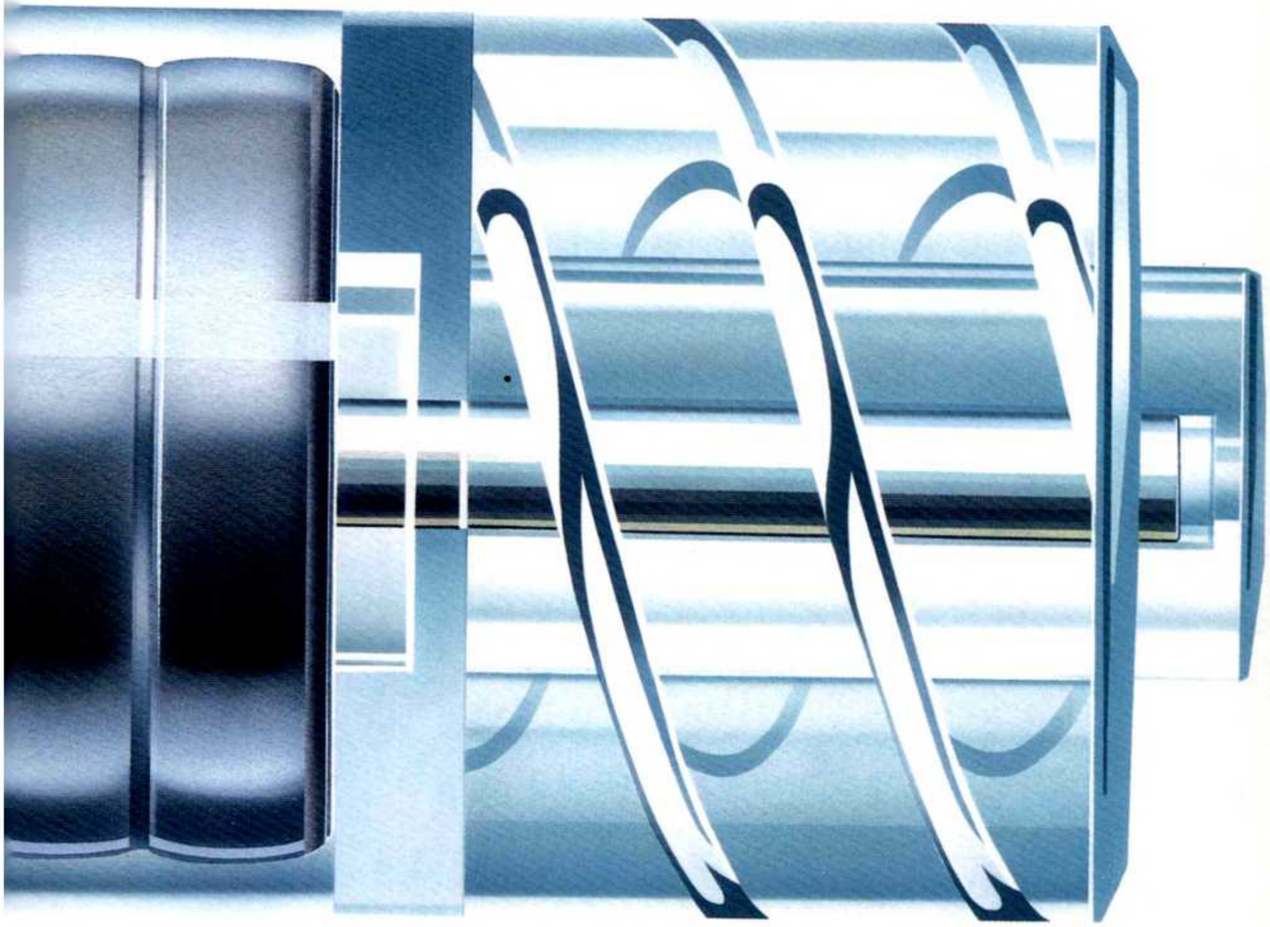

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Are severe acute retinopathy of prematurity and severe periventricular leucomalacia both ischaemic insults?

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SUMMARY Over a period of 20 months six preterm infants have been seen who developed severe acute retinopathy of prematurity (ROP) and who also had ultrasound evidence of extensive cerebral parenchymal changes compatible with severe periventricular leucomalacia. Only one of these infants had a birthweight of less than 1000 g, and their gestational ages ranged from 27 to 30 weeks. The association between these two important complications of preterm birth has led us to postulate that an episode of hypoperfusion of the cerebral circulation sufficient to result in cerebral ischaemia could also reduce an already compromised ocular blood flow and further exacerbate retinal ischaemia, thereby increasing the severity of ROP.

Periventricular leucomalacia (PVL), and retinopathy of prematurity (ROP) are both important common complications of preterm birth. Over a two-year period we have noticed the association of severe acute ROP with extensive cerebral intraparenchymal lesions. Both conditions are thought to be ischaemic in nature, and in this article we explore the possibility that the insult responsible for the cerebral ischaemia could also increase the severity of the retinopathy.

Patients and methods

All infants in two neonatal intensive care units (Leicester Royal Infirmary and Nottingham University Hospital) have regular cranial ultrasound scans and ophthalmic examinations. All scans are performed with a real-time sector scanner, fitted with a 5 MHz or 7·5 MHz transducer. Eye examinations are carried out at weekly intervals from 3 weeks of age, by one of us (ARF) using indirect ophthalmoscopy, speculum and scleral indentation, following pupillary dilatation with 0·5% cyclopentolate eyedrops.

Results

Over a period of 20 months 299 infants were examined in the two neonatal units, and six infants were found to have extensive cerebral parenchymal abnormalities together with severe ROP. The records of each of the six infants were examined, and seven indicators of neonatal illness were extracted. These were an Apgar score <5 at 5 minutes, the duration of assisted ventilation, the occurrence of pneumothorax, the presence of a persistent ductus arteriosus (PDA) requiring treatment, proved septicaemia, exchange transfusions, and the number of blood transfusions. Many factors have been reported to be associated with ROP, and include some of those described above.

Each of the six patients was matched with an infant of the same gestational age who had sustained so far as practically possible the identical indicators of neonatal illness listed above. Cranial ultrasound findings and severity of ROP were noted for both groups of infants. The details of both groups of infants are summarised in Tables 1 and 2. Four of the six study infants had clinical evidence of an episode of circulatory collapse. All six of the study patients had intraventricular haemorrhage (IVH) with echodensities in the periventricular areas and subsequent cyst

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Table 1 *Details of the six study infants*

Patient	*1*	*2*	*3*	*4*	*5*	*6*
Gestational age, weeks	30	28	29	29	29	27
Birth weight, g	1440	910	1340	1360	1130	1300
Apgar score at 5 min	3	10	8	?	7	3
Duration of IPPV, days	10	1 hour	10	6	46 hours	17
Pneumothorax	Bilateral	None	Right	None	None	None
Transfusions	8	8	3	3	2	4
PDA	Yes	Yes	Yes	No	No	No
Exchange transfusion	No	Yes	No	Yes	No	No
Septicaemia	No	No	No	No	No	No
Cranial ultrasound	IVH CPVL V dil (shunt)	R IVH CPVL V dil (shunt)	R IVH Por cyst V dil (LPs)	L IVH Por cyst V dil (LPs)	L IVH CPVL, SCL	R IVH Por cyst V dil (shunt)
Acute ROP, grade: Right	3	3+	3	4	3	3
Left	3	3+	4	4	3	3
Cicatrical ROP grade. Right	2	2	1	5	0	2
Left	2	0	5	5	0	1

IPPV=intermittent positive pressure ventilation. PDA=persistent ductus arteriosus requiring therapy. IVH=intraventricular haemorrhage. CPVL=cystic periventricular leucomalacia. Por cyst=porencephalic cyst. SCL=subcortical leucomalacia Shunt=insertion of ventriculo-peritoneal shunt LPs=serial lumbar punctures V dil=ventricular dilatation

formation with ventricular dilatation. Five required treatment for progressive ventriculomegaly. Among the comparison group of infants four had IVH without periventricular echodensities and two developed ventricular dilatation, one of whom required a ventriculoperitoneal shunt. One infant (comparison infant 5) was found to have an area of echodensity in the periventricular white matter. This persisted for more than two weeks, but cysts did not develop. One infant in the comparison group had normal ultrasound scans throughout.

The eye findings are shown as the most severe grade of acute and cicatricial ROP in each eye (Tables 1 and 2). The grading system used is that of the International Classification of ROP.[1] Four of the patients we are reporting on had stage 3 acute ROP, one had stage 4 in both eyes, and the sixth had stage 3 in the right and stage 4 in the left eye. In the comparison group four infants had acute ROP stage 1 and two infants had normal eyes. None of this group developed cicatricial ROP.

Arterial oxygen readings (PaO_2) for each infant were analysed. A curve was plotted for PaO_2 against the time of sampling for each infant. The area under the curve was measured above a level of 15 kPa and also below that level, as illustrated in Fig. 1. The area above (area A) expressed as a proportion of the total area above and below 15 kPa (area A+B) can be used as an estimate of the proportion of time above this level and also takes into account the severity of

Table 2 *Details of the six study infants in the comparison group*

Comparison patient	*1*	*2*	*3*	*4*	*5*	*6*
Gestational age, weeks	30	28	29	29	29	27
Birth weight, g	1320	720	1370	1020	1200	830
Apgar score at 5 min	8	8	6	6	8	8
Duration of IPPV, days	9	0	7	7	2	18
Pneumothorax	Bilateral	None	Left	None	None	None
Transfusions	1	8	1	4	1	4
PDA	Yes	Yes				Yes
Exchange transfusion	No	No	No	No	No	No
Septicaemia	No	No	No	Yes	No	Yes
Cranial ultrasound	IVH	Normal	IVH V dil (shunt)	IVH	Prolonged flare	IVH V dil (no treatment)
Acute ROP, grade	1	Normal	1	1	Normal	1
Cicatrical ROP grade	0	0	0	0	0	0

IPPV=intermittent positive pressure ventilation PDA=persistent ductus arteriosus requiring treatment IVH=intraventricular haemorrhage. Shunt=insertion of ventriculo-peritoneal shunt Prolonged flare=echodensity in periventricular region persisting for more than two weeks which did not develop into cysts. V dil=ventricular dilatation.

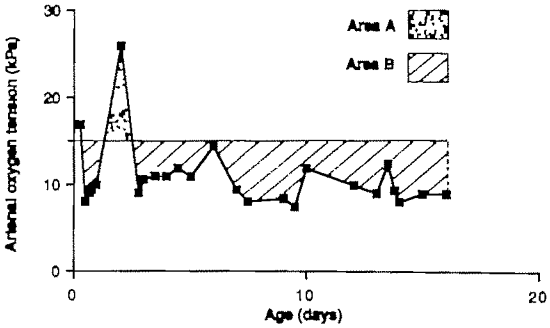

Fig 1 *Graph of arterial oxygen tension plotted against age, for study patient 4, to illustrate method of estimating hyperoxia Hyperoxia estimate=area A/area A+B.*

hyperoxia. In both groups the median proportion of time above 15 kPa was 0·02, and there was no significant difference between them (p=0·69, Mann-Whitney U test).

Discussion

We have presented the details of six infants and six comparison infants who were matched for gestational age and seven indicators of neonatal illness. The comparison group did not suffer ischaemic brain damage, and four of the six developed mild acute ROP, whereas all six of the patient group suffered severe cerebral intraparenchymal lesions and all six developed severe acute ROP. Complete resolution occurred in only one (case 5), and the remaining five account for all but one of the most severe cases of cicatricial ROP seen in the 299 babies examined in the two neonatal units in question over the 20-month period of this study. These infants therefore represent an unusually severe subgroup, and it is interesting to note that only one of the six had a birthweight under 1000 g, a group recognised to be particularly at risk of ROP.[2,3]

From these observations we have developed a hypothesis which may explain the severity of ROP in our infants. It is generally acknowledged that ROP has an ischaemic basis, but we suggest that these infants suffered an additional ischaemic event, further upstream in the carotid circulation, resulting in the cerebral ischaemic lesion, periventricular leucomalacia, and a significant increase in the severity of acute ROP.

There have been many reported associations of neonatal events with the occurrence of ROP, of which oxygen exposure is the best known. We analysed the recorded arterial oxygen values of the six study infants and of those in the comparison group and found that there was no significant difference between them when the area under the PaO_2 curve was used to measure the degree of hyperoxia experienced by the infants. Hyperoxia is difficult to quantify over a prolonged period in a rapidly changing clinical situation, and the method we used is open to criticism for oversimplification, as PaO_2 levels fluctuate and the sampling intervals are necessarily variable. Despite these clinically inevitable shortcomings, this method has provided an estimate of documented hyperoxia and allowed comparison between the two groups. It is recognised that not all infants with hyperoxia develop ROP,[4] and other factors apart from oxygen are also important, such as the severity of illness in the neonatal period.[5,6]

Intraventricular haemorrhage has been reported in association with ROP by Procianoy *et al.*[7] They diagnosed IVH by computerised cranial tomography but did not describe periventricular changes, though some of their patients did have ventricular dilatation. Since then the use of ultrasound imaging has become more precise, and characteristic appearances of PVL have been described in detail.[8] PVL occurs in the so-called watershed regions within the periventricular white matter least well supplied by the developing arterial circulation. These areas are particularly susceptible to a critical fall in cerebral perfusion.[9] There is now a body of evidence to support the suggestion that most intraparenchymal 'haemorrhagic' lesions are also basically ischaemic in nature, with secondary bleeding into infarcted areas.[10 11] Four of our patients showed the classical ultrasound appearance of cystic PVL[8] together with intraventricular haemorrhage. There was clinical evidence of circulatory collapse in four infants, and the cranial ultrasound appearances in all six infants are compatible with severe ischaemic infarction.

The retina of full-term infants is supplied by both the choroidal and retinal vessels, but in the fetus this is not so. The retinal vasculature begins to develop only at the 16th week of intrauterine life[12] and progresses centrifugally from the optic disc, reaching the temporal periphery just after term. During early fetal life the retina receives its nutrients from the choroidal circulation, and although this contribution decreases as the retinal vasculature develops the choroid continues to supply the outer portion of the retina throughout life. Since ROP develops at the junction of the vascularised and yet-to-be vascularised retina, it occurs in an area particularly vulnerable to changes in blood flow. Lucey and Dangman[5] have described two infants who developed severe blinding ROP. In one of these infants there was no cerebral blood flow for seven minutes and the other suffered a cardiac arrest for several minutes. These authors considered that the severe ROP seen in these two infants could be due to cerebral and retinal hypoperfusion.

Our patients were matched as closely as is clinically possible in a retrospective study with those in the comparison group for seven indicators of neonatal illness. Although severe ROP and severe cerebral ischaemic changes may be associated merely as two unrelated consequences of severe illness in the preterm infant, these conditions could be related through a final common pathway initiated by ischaemia.

An ischaemic hypothesis for the production of ROP was first suggested by Rubinstein in 1952[13] and is an essential component of the theory proposed by Ashton *et al.* in 1953[14] and discussed again by Ashton in 1980.[15] These authors showed that destruction of growing retinal vessels by oxygen, the vaso-obliterative phase of ROP, rendered the retina ischaemic and led to the vasoproliferative phase. In a recent review Garner and Kissun[16] stated that 'there is now direct as well as indirect support for the concept that proliferative retinopathy is a consequence of impaired retinal circulation.' Hungerford *et al.*[17] also suggested that ROP and cerebral damage may both have an ischaemic basis. Twenty-five years ago Banker and Larroche[18] noted an association between spastic diplegia due to PVL in preterm infants, and they postulated that ischaemic damage secondary to oxygen toxicity might be the final common pathway in both conditions.

Retinal ischaemia is recognised as the likely basis of ROP, and four of six of the comparison group developed minor retinal changes. Yet although the patient and comparison groups were clinically matched, and there was no significant difference in the oxygen exposure to the two groups, our six patients unlike the six 'controls' developed both severe ROP and cystic PVL. Additional factors must be involved. Both the cerebral and ocular circulations arise from the internal carotid artery, and therefore an episode which causes hypoperfusion of the cerebral circulation sufficient to result in cerebral ischaemia could also reduce an already compromised ocular blood flow. Although the retinal vessels are capable of autoregulation, the choroidal circulation is not,[19 20] with the consequence that, when there is a reduction of flow in the carotid artery, flow through the choroidal system could also fall, thereby exacerbating ischaemia of the overlying retinal tissues—essentially the mechanism suggested for the two patients of Lucey and Dangman.[5]

We are not proposing that ischaemia due to cerebral hypoperfusion is the sole cause of ROP; indeed four of the comparison infants who did not suffer cerebral ischaemia developed mild acute ROP. But cerebral hypoperfusion resulting in ischaemia is considered to be the basis of PVL, and we suggest that in some infants it may also exacerbate the already ischaemic retina and be a major factor contributing not to the initiation but to the severity of the retinal condition.

We are grateful to Professor D Hull for allowing us to report two of the patients under his care We thank Mr D E Shaw for his help with analysing the data and Mrs M Hopson for secretarial assistance

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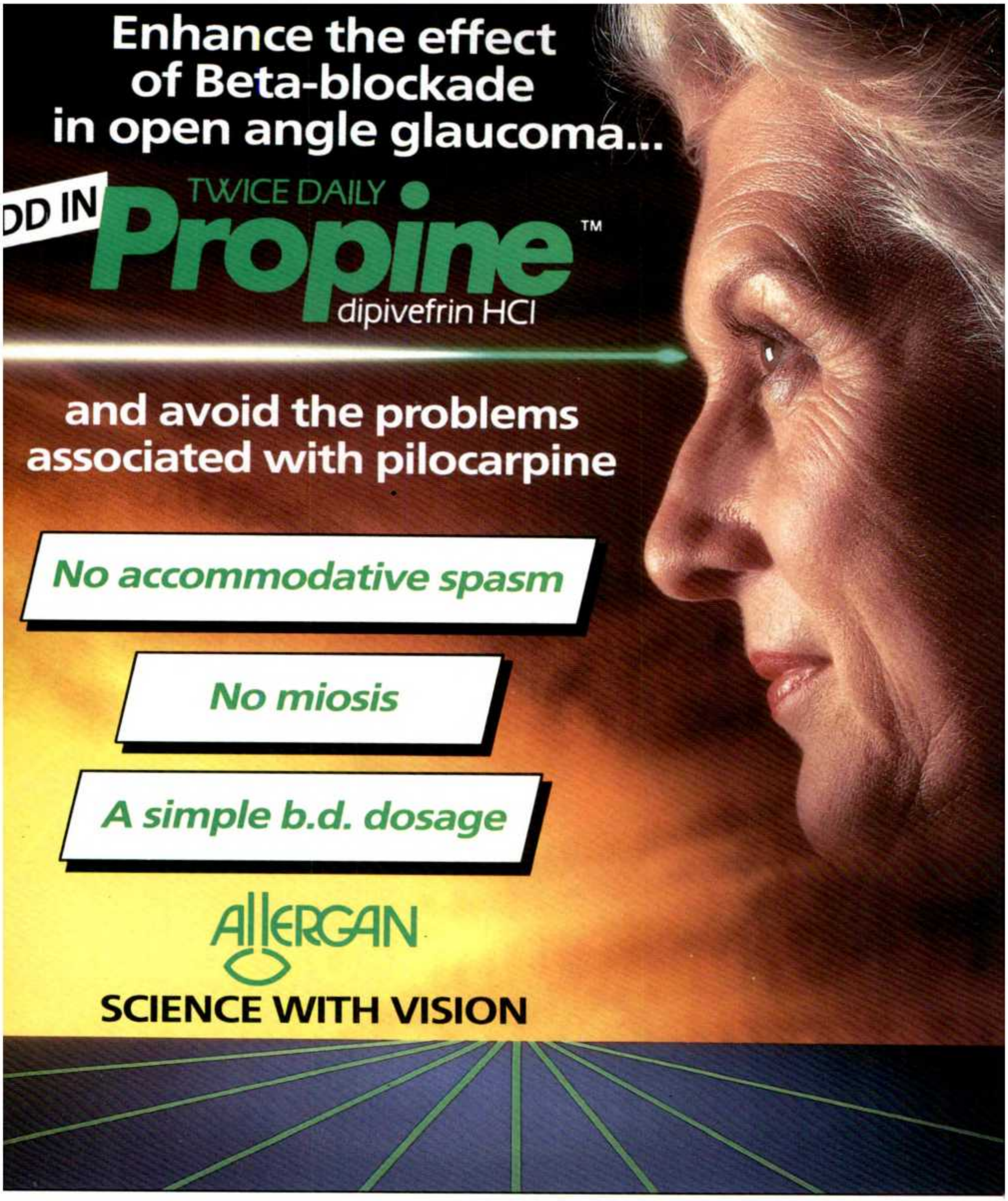

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British Journal of Ophthalmology, 1989, **73**, 115–120

Photoaversion in retinitis pigmentosa

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SUMMARY Photoaversion, or light-induced interference with visual comfort and performance, has been a recognised but poorly documented symptom in retinitis pigmentosa (RP). We found that a majority of our RP patients complained of photoaversion even in the absence of significant cataract. RP patients had reduced contrast sensitivity relative to normal people, but the decrement in their visual performance as a result of glare or photostress was only slight. RP patients had raised short-term adaptation and increment threshold levels, but their rate of short-term or photopic adaptation was normal. Photoaversion in RP may result because a small interference with contrast sensitivity or adaptation can place patients in a range of functional disability, or it may derive from a combination of minor aberrations.

The most prominent symptoms of retinitis pigmentosa (RP) are progressive night blindness and field loss, though central vision may also be reduced. Many patients complain of difficulty in functioning in bright light (noted anecdotally by Leber in 1916[1]), but to our knowledge there has been no documentation of the frequency, characteristics, or physiology of such symptoms.

This report represents a preliminary attempt to characterise photoaversion in RP, which we define as symptomatic interference with visual performance due to exposure to bright light. RP patients were surveyed to discover the frequency and nature of complaints, and presented with a variety of psychophysical tests to define and quantify the symptom of 'photoaversion'.

Material and methods

A total of 20 photoaversive RP patients (11 male, 9 female) performed psychophysical tests (though no subject performed all tests). The age range was 11–68 (average 34); visual acuity ranged from 20/20 to 20/70. RP was documented by history, fundus examination, ring scotoma, and electroretinography; no patients had more than a trace of posterior subcapsular opacity. The normal controls were 16 subjects (aged 16–63, average 33) with no ocular pathology, no visual complaints, and 20/20 or better acuity.

To survey for symptoms we contacted personally all our RP patients whose records (within 10 years) indicated 20/200 or better acuity and basically clear media, and who could be reached within a two-week study period. A total of 22 reported functional reading ability and no cataract to their knowledge; seven were in the group undergoing experimental studies. We also surveyed 19 normal people of similar ages.

CONTRAST SENSITIVITY AND GLARE TESTS

Contrast sensitivity at distance was measured monocularly, in the presence and absence of glare, with Vistech charts (Vistech Consultants, Inc.). These consist of three large posters with sine-wave gratings of varying spatial frequency and contrast whose orientation may be vertical or tilted.[2] Illumination was as in the manufacturer's specifications. The chart was viewed through a circular 22 W fluorescent bulb (GTE Sylvania), 6 inches (15 cm) from the face, which served as a source of glare.

Glare sensitivity was also evaluated with the Miller-Nadler Glaretester, a tabletop viewer that presents a 20/200 Snellen-equivalent black Landolt ring[3] surrounded by a circular field of variable darkness within a 6850 cd/m^2 glare field. Subjects were positioned 33 cm from the screen, and asked to

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report the ring's orientation as a function of contrast with its surround. For a subgroup of subjects the results were compared with those with the glare field masked by cardboard.

Further glare and photostress studies were performed with the Vistech Multivision Contrast Tester (Vistech Consultants, Inc.). This apparatus provides variable illumination and glare (central or peripheral) with a set of small Vistech contrast sensitivity targets and Snellen acuity letters viewed through a binocular eyepiece. To measure macular photostress, subjects were adapted to a background illumination of 18·8 cd/m^2 for 60 seconds and Snellen acuity measured; subjects then fixated on a 5820 cd/m^2 central light source for 15 seconds, and the time was noted to recover within 1 line above original acuity. To evaluate peripheral glare, the intensity of peripheral illumination was raised from 1·7 cd/m^2 to 240 cd/m^2 for 60 seconds, and the time noted to recover within 1 line of original acuity. To estimate 'discomfort' from bright light, we began with a background illumination of 19 cd/m^2 and increased glare illumination at a steady rate. The subjects were asked to indicate 'when the light reaches a level that makes you feel like squinting'. This test was performed monocularly and binocularly, and with peripheral and central glare; for each condition the average of three trials was used.

DARK ADAPTATION TESTS

We studied the early time course of adaptation by an established technique[4] for measuring threshold within a fraction of a second before or after shutting off an adapting background light. A Maxwellian view optical system presented a 2·5°, 20 millisecond, red test flash within an 8·5°, 5·5 log troland, yellow background. The intensity of the test flash was varied with a neutral density wedge. An electric shutter shut off the background at T=0·8 second, and test flashes were presented between T=0·0 and 1·70 seconds. The subject was asked to signal when the test flash was detected. Visual threshold was defined as the intensity at which the target was perceived 50% of the time.

Intermediate rates of dark adaptation were measured with a Goldmann/Weekers Adaptometer. Subjects viewed binocularly the variable intensity light source behind a ground glass diffuser. Target intensity was continuously and alternately increased or decreased until the subject indicated the light was just visible or invisible. Subjects were preadapted at low photopic levels (68·5 cd/m^2) for 2 minutes, and then a bright background light (1370 cd/m^2) was turned on for 3–5 minutes. Lighting was then returned to the original background level.

Results

PHOTOAVERSION AS A SYMPTOM

Twenty-two RP patients without cataracts and 19 normal subjects were asked the series of questions shown in Fig. 1. The great majority of RP patients indicated they were sensitive to light and had difficulty adjusting from outdoor to indoor illumination. Few normal people had trouble in the sun or difficulty with adaptation for more than 30 seconds, though they were nearly as likely as RP patients to be bothered by oncoming headlights at night. Almost all

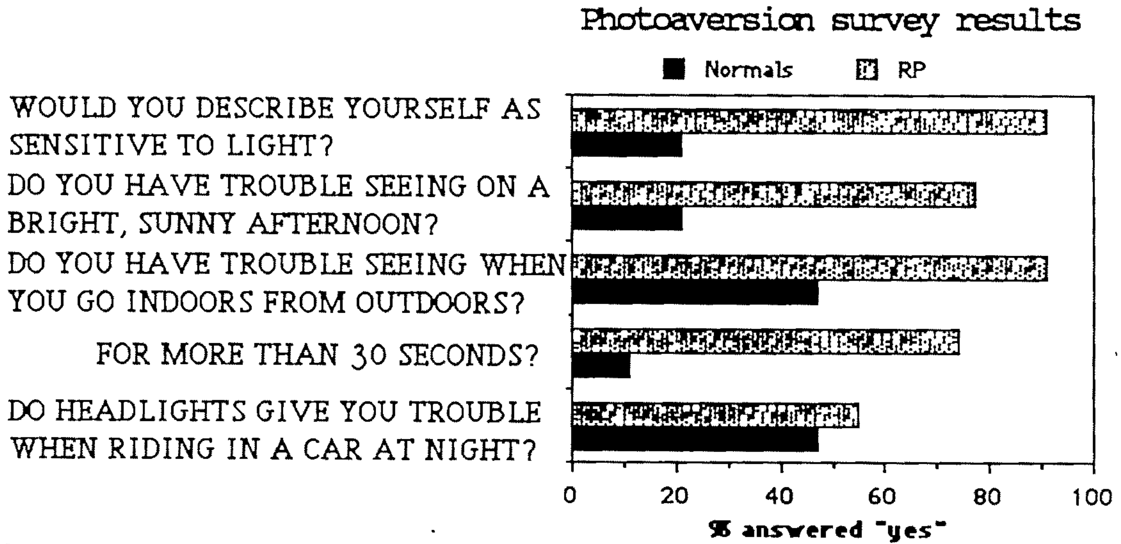

Fig. 1 *Answers from the survey of RP and normal subjects.*

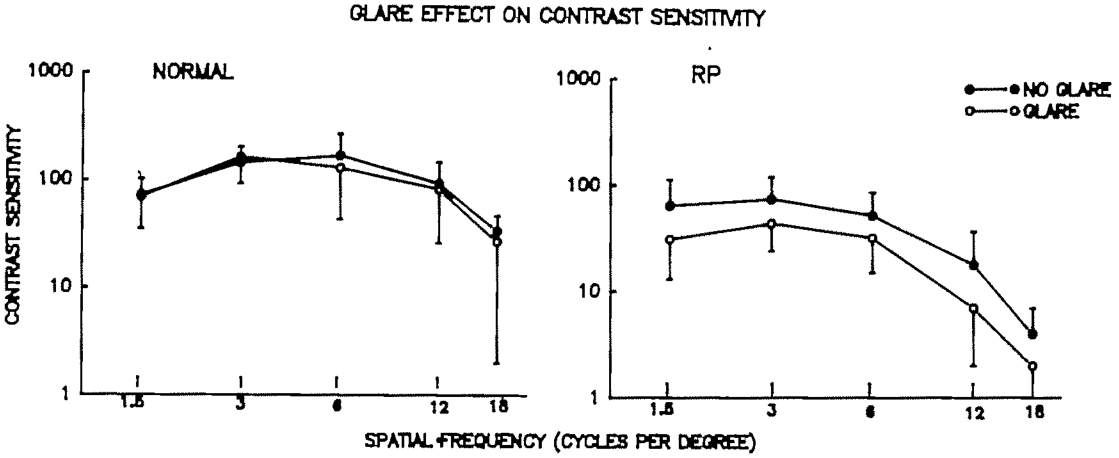

Fig. 2 *Contrast sensitivity data, with and without glare, for RP and normal subjects Error bars are ±1 standard deviation.*

(17 of 20) of the light sensitive RP subjects cited bright sun as one of the worst situations for daytime vision, with overcast or shadows less frequently cited. There was no clear consensus, however, as to whether the trouble in sunlight lasted just a few minutes or for the entire time of exposure. Only three RP patients did not wear an aid against bright light (cap, sunglasses, or a visor). The photoaversive RP patients most often complained of light as irritation, pain, or a cause of tearing; the four photosensitive normal persons noted headache or squinting.

CONTRAST SENSITIVITY AND GLARE SENSITIVITY

The contrast sensitivity of seven RP patients and seven normal controls was tested at 10 feet (3 m) with Vistech posters while looking through a circular fluorescent bulb as a source of peripheral glare. Fig. 2 shows contrast sensitivity (plotted against spatial frequency) with the light on and off. RP subjects showed lower contrast sensitivity than normal people under either condition, and a roughly 0·1 log unit greater decrement in contrast sensitivity in the presence of glare. Further to evaluate glare effects we tested nine RP and six normal subjects using the Miller-Nadler glaretester. Normal people had little difficulty with the test (only one missed one target), and the RP patients on average missed only the two most subtle targets in the presence of glare, corresponding (according to manufacturer's data) to a 5% glare disability. With the peripheral glare source masked off, a subgroup of six RP and four normal subjects recognised all of the targets.

DISCOMFORT AND PHOTOSTRESS

The results of central photostress and peripheral bright light testing of nine normal and four RP subjects are presented in Fig. 3. The scattergrams show the time for recovery of vision to 1 line above normal acuity. The RP patients generally had longer recovery times; after peripheral light exposure all the normal persons recovered visual function immediately, whereas only one of the four RP subjects had no period of delay. The scattergrams in Fig. 4 show the intensity of binocular illumination, presented either centrally or peripherally, at which subjects perceived discomfort. The discomfort levels of normals versus RP patients were not categorically different, and some RP patients were even more tolerant of bright light than the controls (despite the general complaint of photoaversion). Results from monocular testing were similar.

DARK ADAPTATION IN PHOTOSENSITIVE SUBJECTS

Data on the first 1–2 seconds of dark adaptation from five RP patients and seven normal subjects are presented in Fig. 5. RP subjects had higher thresholds than normals both before and after turning off the adapting light; however, the *rate* of early dark adaptation differed very little, if at all. We also tested (for three RP subjects and two normals) the speed of adaptation between levels of photopic background illumination roughly 2 log units apart (Fig. 6). RP patients had higher baseline thresholds at either level of illumination than normal people, but the recovery of sensitivity on lowering the background intensity was almost immediate for both groups.

Discussion

Clinicians are aware that many RP patients complain bitterly of visual impairment or of discomfort in bright light, but we could find no reports on the

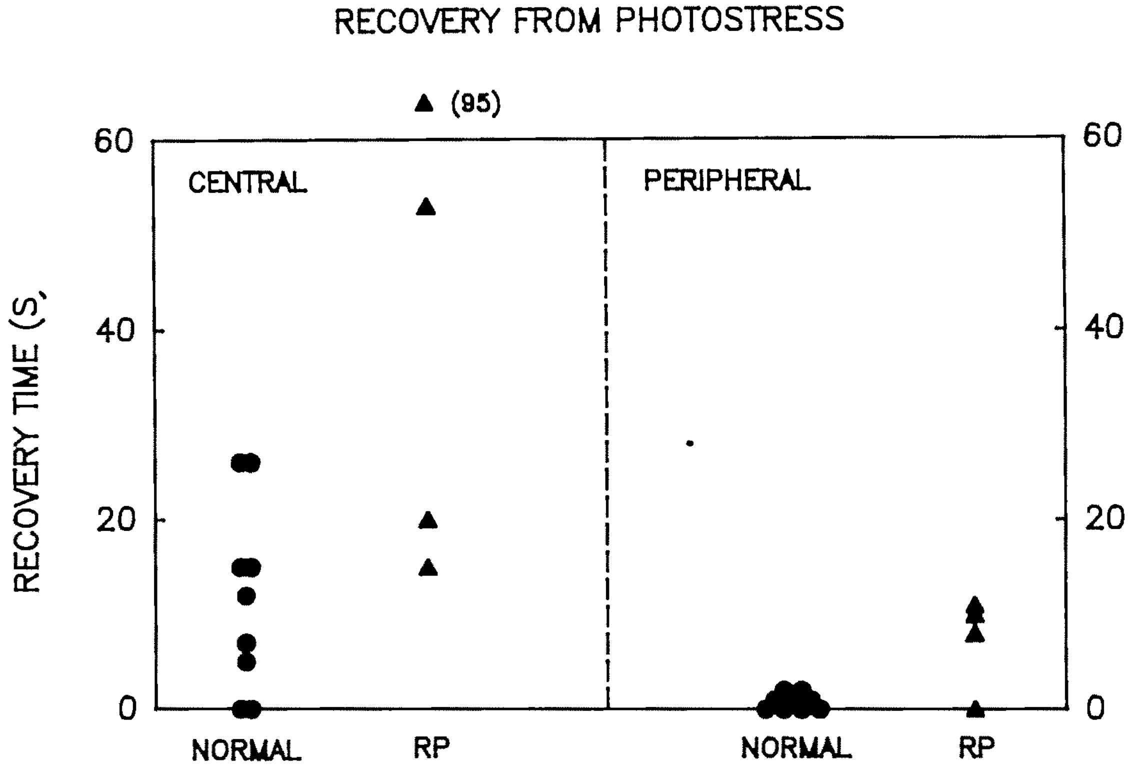

Fig. 3 *Times for recovery from central photostress and peripheral light exposure for RP and normal subjects.*

frequency or severity of this symptom or its pathophysiology (in the absence of a scattering source such as cataract). This report represents a preliminary attempt at resolving these issues. The number of patients studied was small, but our purpose was to seek major differences between RP patients and normal persons and study as many conditions as possible, rather than to evaluate any specific test exhaustively.

Our survey confirms the clinical impression that

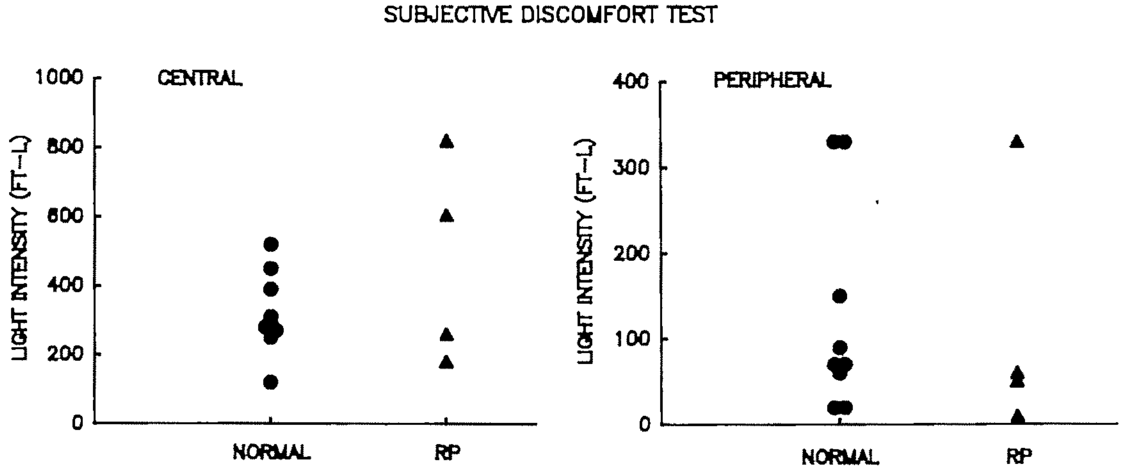

Fig. 4 *Light intensities of central and peripheral glare sources that caused subjective discomfort in RP and normal subjects. (SI conversion: foot-lambert×3·426=candelas per square metre.)*

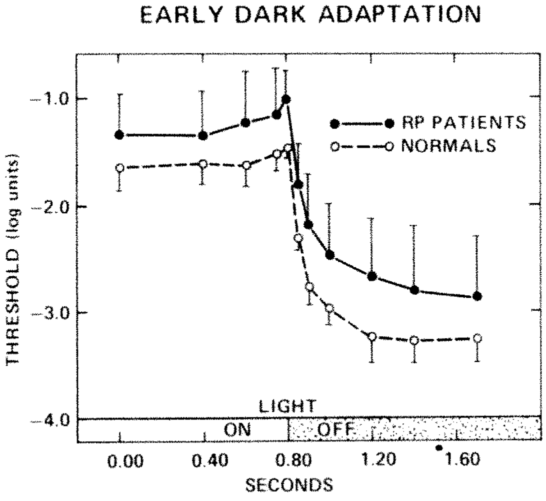

Fig. 5 *Early dark adaptation data for RP and normal subjects. Error bars are ±1 standard deviation.*

photoaversion is a significant complaint in RP independent of symptoms from cataract. We have used the term 'photoaversion', since 'light sensitivity' is somewhat ambiguous (sensitivity refers to both thresholds and discomfort) and 'photophobia' is used for conditions that produce pain such as iritis. We asked patients about 'sensitivity to light', but the meaning is unambiguous in this colloquial context. Nearly all the 22 RP patients surveyed considered themselves to be light-sensitive, had difficulty in functioning in bright sun, and had difficulty recovering sensitivity after such exposure. Our psychophysical results show that it is not so easy to find quantitative confirmation or definition of these subjective symptoms.

Our study of visual recovery from photostress showed that RP patients require a longer time to recover visual acuity following a bright stress (either peripheral or central) than normal persons. However, we could not detect any difference between

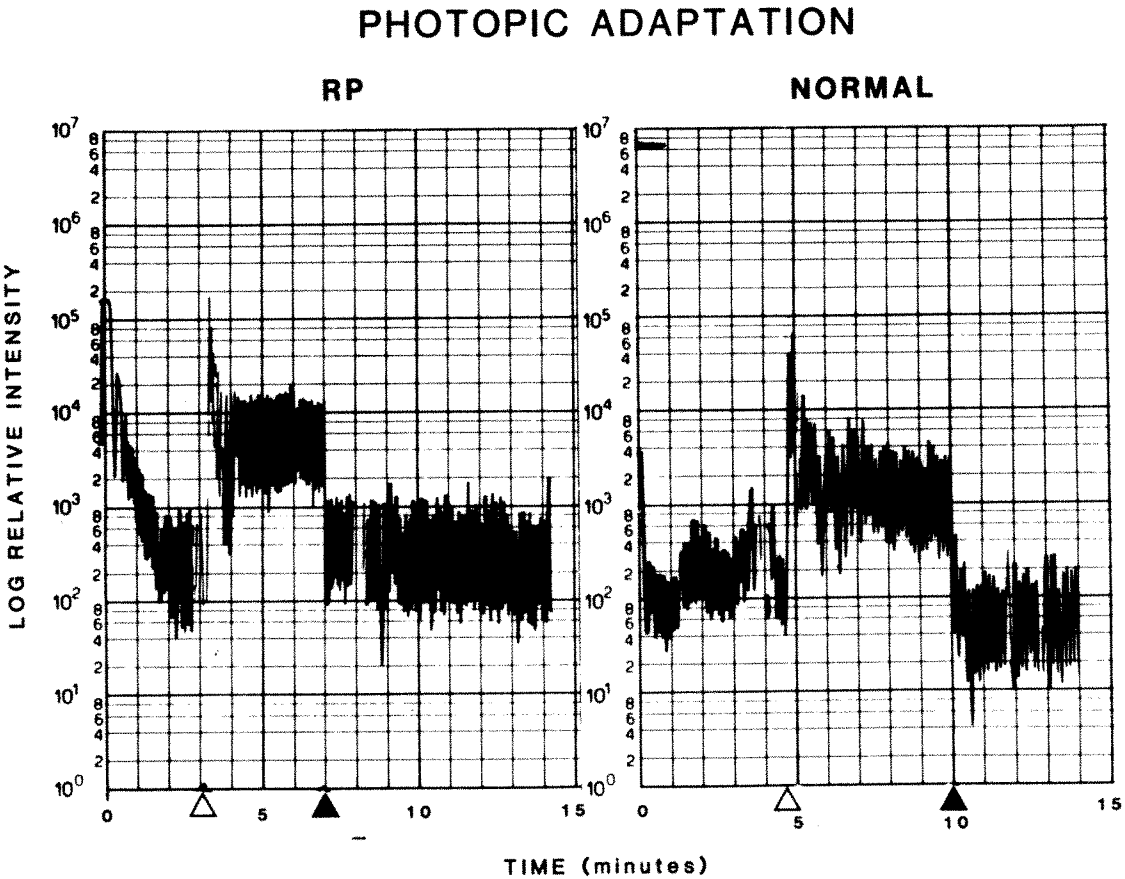

Fig. 6 *Representative tracings of adaptation between two levels of photopic illumination for a normal and RP subject (20 ft-L (68·5 cd/m^2) at start and finish; 400 ft-L (1370 cd/m^2) between the arrows).*

patients and normals in the rate at which dark adaptation began. The common complaint of difficulty coming indoors may be explained by the fact that RP patients require a greater degree of adaptation before their vision finally (if ever) reaches a functional level, even though the actual rate at which photopic dark adaptation proceeds is not unusual.

The functional difficulties which RP patients describe in bright light are harder to explain. Contrast sensitivity was reduced by bright light somewhat more in RP subjects than in normal people, but this difference seems unlikely to account by itself for the symptoms of photoaversion. Furthermore, our subjective discomfort test did not indicate that patients were more sensitive to bright light than normal people despite the subjective complaints. Possibly the symptoms derive from the fact that baseline contrast sensitivity is reduced in RP,[5-7] so that even a minimal further reduction due to bright light may move the patient into a range of functional disability. In other words the problem may be less one of supersensitivity to light than one of limited capacity to suffer a small light-induced decrement of function that would normally be tolerated.

Photoaversion in RP is probably not a simple consequence of photoreceptor saturation or photochemical responsiveness, since subjective discomfort levels and adaptation rates were grossly normal. The symptoms cannot be attributed to cataract, since our subjects lacked this complication—though cataract may add to the difficulties experienced by RP patients. It is possible that our studies missed relevant levels of light intensity or wavelengths in outdoor illumination which we could not duplicate in our indoor experiments. It is also quite possible that photoaversion does not, as a symptom, derive from a single physiological source, but is in fact a composite of a number of causes including glare, photostress, low discomfort threshold, altered increment threshold, and poor baseline contrast sensitivity.

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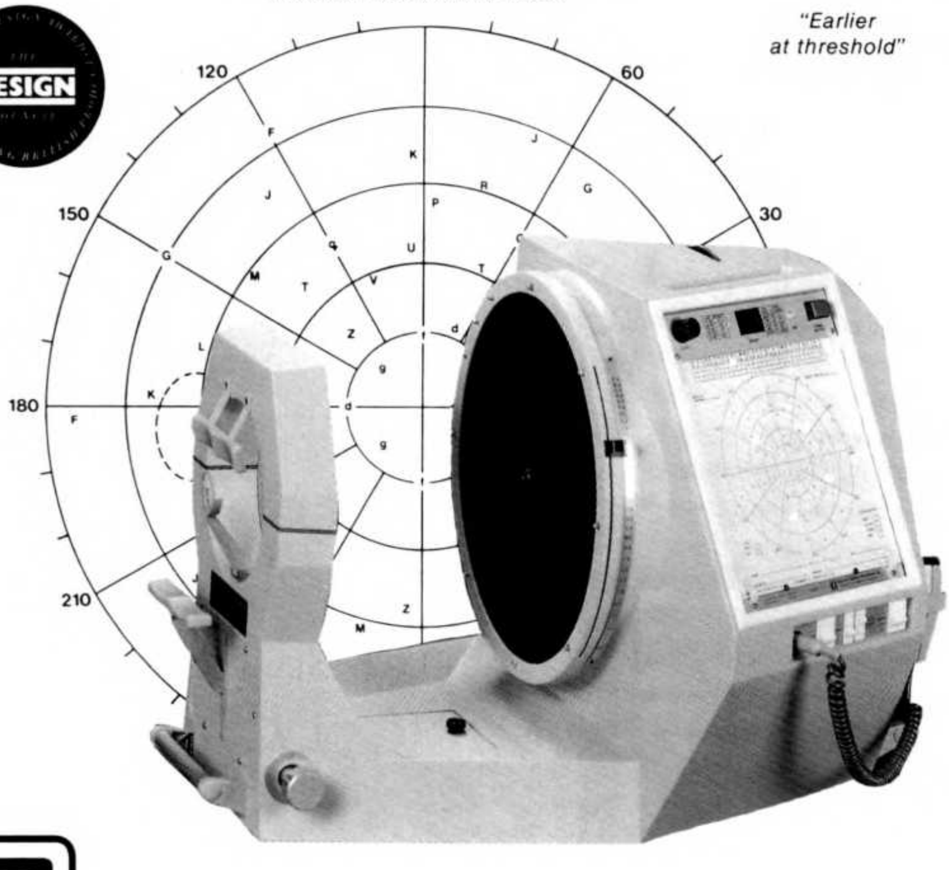

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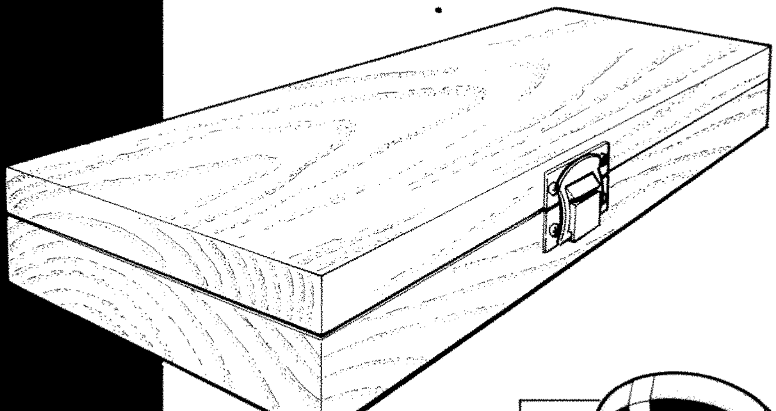

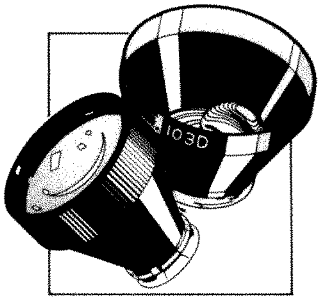

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British Journal of Ophthalmology, 1989, **73**, 121–125

Posterior corneal folds and endothelial cell damage in human donor eyes

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SUMMARY Posterior folds in human donor corneas stored as whole eyes in moist chambers, or isolated in McCarey-Kaufman medium at 4°C, have been studied by light and scanning electron microscopy to determine whether or not endothelial cells on the folds are damaged. Extensive, often irreversible cell damage was found associated with most of the folds. Hence posterior folds in donor corneas are of importance in that they indirectly reduce the quality of the donor cornea for transplantation.

The condition of the corneal endothelium of human donor eyes at the time of transplantation has a great bearing upon the results of grafts for which they are used. At present the state of the endothelium is judged by slit-lamp and contact specular microscopical examination of its mosaic in the intact eye. Further assessment of McCarey-Kaufman (MK) stored corneas can be made with the Eye Bank specular microscope and video system (Product Research Organisation, Inc Tustin, California, USA) immediately before grafting while the excised cornea is in the preservation medium.

Posterior corneal folds are a well known clinical manifestation of overhydration of human corneas They have been reported in intact donor eyes[1] and in isolated corneas mounted under the specular microscope.[2] They are not apparent, however, in corneas less than two hours post mortem. There is some evidence that endothelial cells incorporated in the folds are damaged—for example, they take up silver nitrate and trypan blue[3][4]—and show morphological changes in a variety of species.

Recently Alfonso *et al.*[5] coined the term 'snailtracks' to describe irregular, discontinuous, greyish white streaks or patches seen at the level of the corneal endothelium in patients after surgical procedures in the anterior chamber. They stated that these tracks could be differentiated easily from Descemet's folds. They noted a similar phenomenon in donor corneas stored in MK medium. From their scanning electron microscopic (SEM) finding of tracks of damaged endothelial cells in the donor corneas they suggested that clinical snailtracks may have relevance as a marker for corneal endothelial cell damage. Investigation of clinical snailtracks by Laganowski and associates[6] failed to reveal significant cell damage. Thus it seems that the tracks seen in corneas in vivo and in vitro are not the same. Endothelial cells on the sloping sides of the posterior folds of donor corneas are invisible to the specular microscope. Therefore in the present study relationships between cell damage and the folds were sought by scanning electron microscopy.

Material and methods

Two paired and four unpaired donor eyes received at the Eye Bank were used for this study. The ocular history was normal in each. All were examined with the slit-lamp and wide field specular microscope (the Pocklington, Keeler/Konan) for the presence of folds. The paired eyes (1 and 2 in Table 1) were enucleated 15 hours post mortem and stored intact for four hours in moist chambers at 4°C before their corneas were excised, with a 2 mm scleral rim, and placed in MK medium at 4°C for 96 hours. The remaining eyes, nos 3, 4, 5, and 6 (Table 1), were left intact suspended in a moist chamber at 4°C—one each for 24, 48, 110, and 120 hours—before corneoscleral buttons were prepared as above.

After their storage in MK medium the paired corneas and the one prestored for 110 hours in a

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Table 1 *Donor information*

Eye	*Age (yr)*	*Sex*	*COD*	*Death to Enucleation*	**Enucleation to SL exam*	*Time in MC at 4°C*	*Time in MK at 4°C*
1	79	M	Bronchopneumonia	15 h	2·5 h	4 h	96 h
2	79	M	Bronchopneumonia	15 h 10 min	2·75 h	4 h	95·5 h
3	63	M	Myelodysplasia	2·25 h	3 h	24 h	—
4	7/52	M	Cot death	4·5 h	2 h	48 h	—
5	76	F	Carcinoma liver	8 h	3 h	110 h	—
6	80	M	Cerebrovascular accident	9 h	3 h	120 h	—

* Enucleation to slit-lamp examination.
MC = moist chamber.
MK = McCarey Kaufman medium.
COD = cause of death.

moist chamber were fixed in gluteraldehyde (3%, pH 7·2), postfixed in buffered osmium tetroxide (1%), dehydrated in ascending graded alcohols, critical point dried, and their endothelial sides sputter coated with gold for examination in a Hitachi S520 scanning electron microscope at 20 kV.

The endothelia of the remaining corneas were removed, flat mounted on glass slides, stained with silver and celestine blue according to the method of Smolin,[7] and examined with the light microscope.

Results

Slit-lamp examination of the corneas of the six human donor eyes at the post-mortem times before storage shown in Table 1 revealed moderate to severe

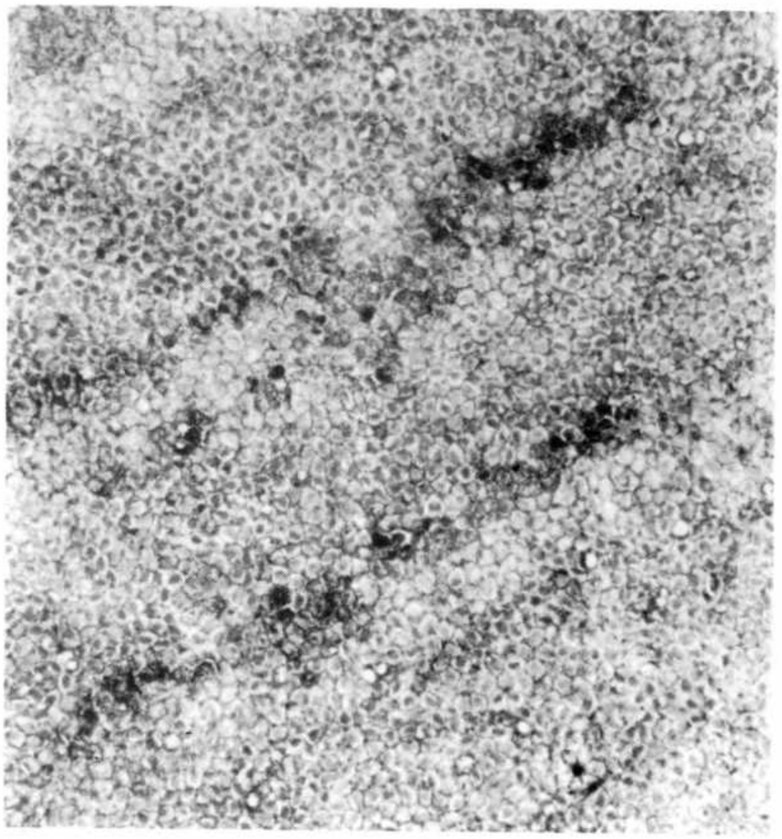

Fig. 1 *Photomicrograph of endothelial flatmount of 7-week-old cornea showing two rows of cells with incorporated silver in an otherwise normal mosaic. Silver and celestine blue. ×150.*

stromal oedema and crisscrossing folds in all quadrants at the level of Descemet's membrane. The folds appeared as greyish white curvilinear opacities in direct illumination or as fine glistening striae in specular reflection. Some of them spanned the entire diameter of the cornea and others extended only from the periphery to the centre. In the 7-week-old cornea (no. 4, Table 1), the folds appeared as parallel lines in contrast to their curvilinear configuration in the adult corneas. Slit-lamp examination of folds at intervals during moist chamber storage showed that they became more numerous with increasing storage time.

SPECULAR MICROSCOPY

Visibility of the endothelium with the specular microscope was limited to small, discontinuous areas between folds on all occasions, and the clarity of the image was reduced by stromal oedema. Visible cells appeared normal with some polymegethism in the older eyes.

LIGHT MICROSCOPY

In the silver 'stained' endothelial flat mounts there were large areas of apparently normal cells with metallic silver confined to the intercellular spaces. There were also bands of cells which were impregnated with silver (Fig. 1), which indicated permeability (and damage) of the cell membranes to silver nitrate. The dimensions and orientations of the bands of cells resembled those of the posterior corneal folds seen before removing the endothelium.

SEM

Obvious features with low magnification SEM were ridges of the posterior corneal surface (Fig. 2). These were considered to be the folds seen with the slit-lamp because their orientations were similar. At higher magnification (Fig. 3) most of the cells away from the folds appeared intact and normal, though a few showed raised central areas (nuclear humps) and partial loss of cell outlines. However, the cells in two or three rows along the crest of most of the folds were apparently irreversibly damaged. Along the major portions of the fold the cell borders were indistinct, the posterior membranes were fragmented, and the cytoplasm was apparently condensed into irregular granules. At the end of the folds surface damage was less marked. The cell borders were still distinguishable and the posterior membranes appeared intact, yet they were deeply indented centrally (Fig. 4) and resembled the denucleated cells described by George, Sourdille, and Bonnaillie.[8]

Discussion

A number of investigators have studied the human

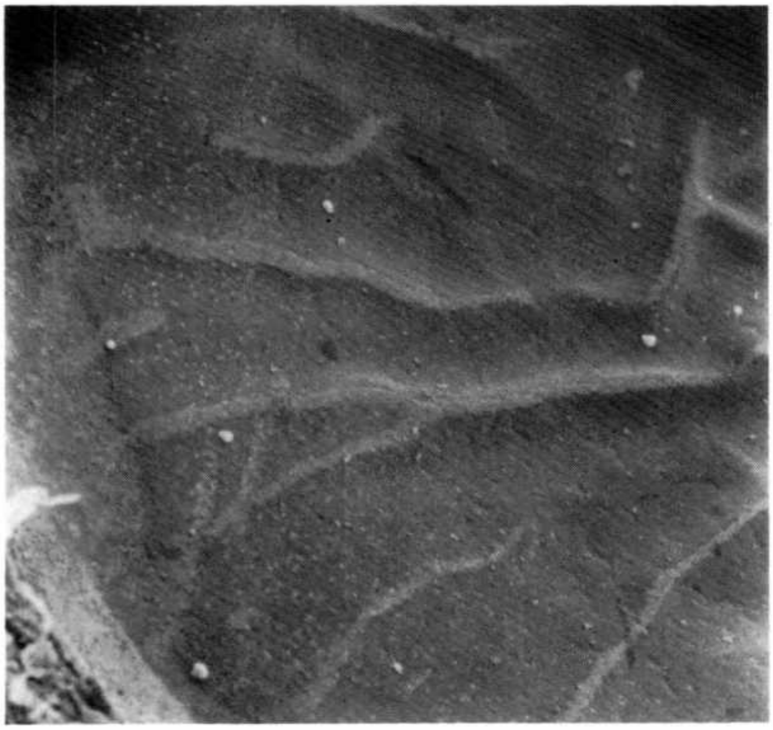

Fig. 2 *Scanning electron micrograph (SEM) of specimen 2 showing folds or ridges in the posterior cornea. ×35.*

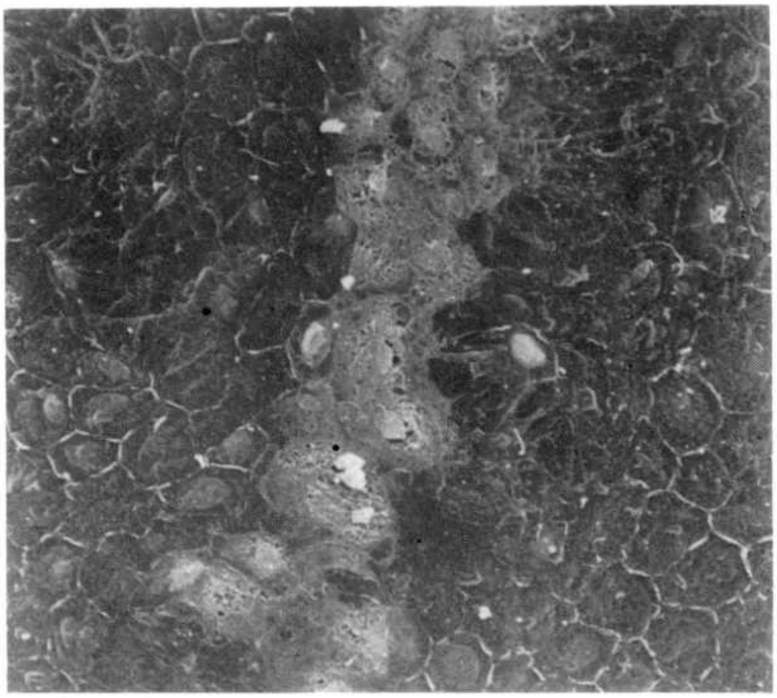

Fig. 3 *Higher magnification SEM of one of the folds in Fig. 2: with irreversibly damaged cells along the crest of the fold and apparently normal cells away from the fold. ×590.*

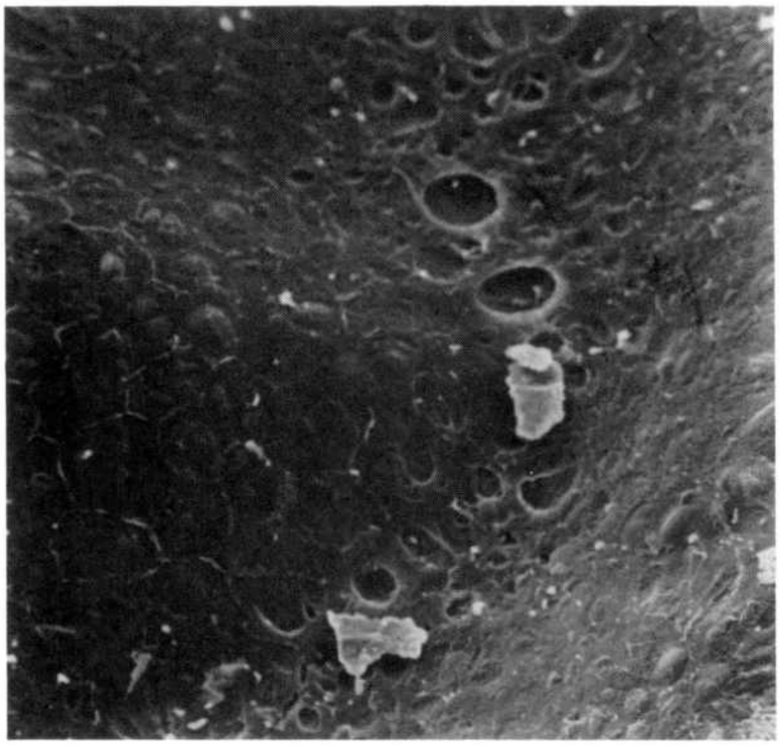

Fig. 4 *SEM of specimen 2 showing 'denucleated' cells towards the end of a fold. ×590.*

corneal endothelium by SEM[9-12] and a normal appearance has been established. The few studies of cells incorporated in posterior folds describe varying degrees of cell damage.[3,4] They and the present study confirm that damaged or dead cells are associated with folds in the posterior layers of corneas in vitro. It follows that, if folds are numerous, the quality of the corneas for transplantation is reduced.

Alfonso *et al.*[5] assumed that the snailtracks seen in vivo and in vitro were the same and that folding was not involved. Laganowski *et al.*[6] found clinical snailtracks to be small folds (wrinkles) with minimal cell damage. Hence it appears that folding in one instance is associated with cell damage and is not in another, and it seems reasonable to assume that either the mechanics of fold formation are different in vivo and in vitro—and result in significant cell damage in the latter only—or that the additional stresses of 'handling' the donor corneas irreversibly damage cells already weakened by the post-mortem folding.

The folds in the posterior layers of donor corneas are undoubtedly a result of post-mortem hydration of the corneal stroma, but the precise reason for their formation is unknown. Roozitalab and colleagues[13] described striae—which are not considered to be synonymous with folds—in donor corneas and believed that they were caused by stretching forces during excision of the corneoscleral button. Grutzmacher *et al.*[14] compared two excision techniques with regard to severity and incidence of endothelial striae and demonstrated that excessive traction results in cell damage or death. In the present study folds were seen with the slit-lamp and specular microscope in all intact donor eyes before careful excision of the corneoscleral buttons. Therefore excessive traction cannot be implicated as the primary cause of the folds. Since, however, the nature of damage to endothelial cells induced by excessive traction by Grutzmacher and associates was similar to that observed by us on the folds in some corneas, without traction, it seems reasonable to suggest that there are at least two mechanisms of inducing endothelial cell damage in donor corneas: (*a*) as a result of the formation of post-mortem folds in the posterior layers of corneas, and (*b*) from excessive traction during excision of donor corneoscleral buttons.

If the maximum number of endothelial cells is to be preserved on donor corneas, it would seem desirable to seek methods to eliminate corneal folding, which itself damages cells, and to avoid traction and distortion of the corneas during excision, which aggravates damage of cells on folds or in the positions of their potential formation. However, there is still no substitute for the freshest donor material possible, and stored material will always inevitably be second best.

We thank Mrs H Taylor for typing the manuscript and the Department of Medical Illustration for the photographic processing.

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Epiblepharon with inverted eyelashes in Japanese children. I. Incidence and symptoms

SACHIKO NODA, SEIJI HAYASAKA, AND TOMOICHI SETOGAWA

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SUMMARY Epiblepharon commonly occurs in Japanese infants and tends to disappear spontaneously with age. We examined 4449 Japanese children aged 3 months to 18 years for epiblepharon associated with inverted eyelashes touching the cornea. The condition was evident in 441 cases. We found that the incidence of epiblepharon decreased with age, but about 2% of high school students still had the condition. No sexual predilection was found. Lower eyelids were commonly involved bilaterally. Most cases of epiblepharon produced no or mild symptoms.

Epiblepharon is characterised by a fold of skin that stretches horizontally across the upper or lower eyelid, usually associated with inversion of eyelashes.[1] It is reported to be common in infants of Oriental races.[1] To our knowledge no report details the incidence of this condition in recent Japanese literature. We therefore examined the incidence and symptoms of epiblepharon in Japanese children.

Subjects and methods

A total of 4449 Japanese children in Shimane Prefecture were examined. Infants were seen on routine 3-month or 6-month screening tests at health centres. Children aged 1 to 6, 7 to 12, and 13 to 18 years were examined on routine ophthalmic screening at nurseries, elementary schools, and high schools, respectively.

Epiblepharon was diagnosed as an extra fold of eyelid skin associated with inverted eyelashes touching the corneal surface. The condition was observed with a binocular loup. Corneal touch was confirmed by topical staining with fluorescein and was inspected in forward, upward, downward, nasal, and temporal eye positions. Epicanthus-like conditions were included in the diagnosis when inverted eyelashes produced corneal touch, because the condition was too difficult to differentiate from epiblepharon. Children who had undergone surgery for epiblepharon were also included, even though the condition had been resolved.

Excluded were cases of true entropion of the eyelid, trichiasis, and distichiasis. To differentiate true entropion, the fold or fold-like skin was pulled down in the lower eyelid or up in the upper eyelid. In cases of epiblepharon the eyelashes were turned out and the normal location of the eyelid margin became visible. In true entropion the entire eyelid margin was pulled outward. Also excluded were cases of corneal abrasion produced by eyelashes associated with microcornea and buphthalmos.

Results

Of 4449 children examined 441 had epiblepharon with inverted eyelashes touching the cornea (Table 1). Four had already undergone surgery. Of 308 infants 142 (46%) were diagnosed with epiblepharon. The incidence of the condition decreased with age: 24% at age 1 year, 20% at age 2 years, 17% at ages 3–4, 7% at ages 5–6, and 2% at ages 13–18 No sexual predilection was found. Table 2 shows the eyelid involvement of all cases of epiblepharon. Lower eyelids were commonly involved bilaterally.

Table 3 indicates clinical symptoms in the 441 cases of epiblepharon. Most children had no complaints (78%) despite corneal touch. The most frequent complaints were tearing or discharge, photophobia, and discomfort or foreign body sensation.

Discussion

It is difficult to confirm the presence of epiblepharon in Japanese children by inspection of the eyelid skin only. We therefore considered an extra fold of eyelid

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Table 1 *Age and sex of children with epiblepharon*

Age (yr)	*Sex*	*No of children examined*	*No of cases of epiblepharon*	*Percent*
0	M	163	73	44·8
	F	145	69	47·6
1	M	152	40	26·3
	F	163	36	22·1
2	M	102	21	20·6
	F	115	22	19·1
3–4	M	287	44	15·3
	F	251	46	18·3
5–6	M	127	9	7·1
	F	101	7	6·9
7–9	M	353	15	4·2
	F	333	14	4·2
10–12	M	251	4	1·6
	F	250	7	2·8
13–15	M	123	3	2·4
	F	129	3	2·3
16–18	M	683	13	1·9
	F	721	15	2·1
0–18	M	2241	222	9·9
	F	2208	219	9·9
Total		4449	441	9·9

Table 2 *Eyelid involvement in 441 cases of epiblepharon*

Eyelid involved	*No of cases (%)*
Unilateral or bilateral	
Unilateral	92 (21)
Bilateral	349 (79)
Upper or lower	
Upper only	31 (7)
Lower only	357 (81)
Upper and lower	53 (12)
Total	441 (100)

Table 3 *Symptoms in 441 cases of epiblepharon**

Symptoms	*No of cases (%)*
No	344 (78)
Yes*	97 (22)
Tearing or discharge	91
Photophobia	84
Discomfort or foreign body sensation	70
Ocular pain	4
Blurred vision	4

*Some cases had multiple complaints

skin plus inverted eyelashes touching the cornea as diagnostic criteria.

During the study we found one case of true entropion, four of trichiasis, one of microphthalmos, and one of buphthalmos in which inverted eyelashes rubbed against the globe. In some children it was very difficult to differentiate epicanthus from epiblepharon Epiblepharon, especially superiorly, may be considered an exaggeration of epicanthus tarsalis.[2]

Our study demonstrated the following findings: (1) epiblepharon commonly occurs in Japanese infants; (2) the condition tends to disappear spontaneously with age; (3) no sexual predilection is evident; (4) lower eyelid involvement is commonly bilateral; and (5) most cases produce no or mild symptoms.

The terminology used to describe entropion, epiblepharon, and epicanthus has been somewhat controversial in Japan. In 1940 Hirose[3] suggested that the inverted eyelashes found in many Japanese infants was a condition distinct from true entropion, and he called it shomo-naihan (Japanese) or entropium ciliare (Latin). Since then entropium ciliare has been widely accepted by ophthalmologists in Japan[4,5] to indicate cases of epiblepharon and some cases of epicanthus. The cases of epiblepharon we observed in the present study represented those of entropium ciliare.

The incidence of epiblepharon in the Japanese population has not been reported recently to our knowledge. Oshima and Nishikawa[5] cited Hashimoto's report from 1926, which indicated that 52·5% of Japanese infants had inverted eyelashes. Similar results (46% of the infants) were obtained in the present study

As shown in our study, most cases of epiblepharon produced no or mild complaints, even though the inverted eyelashes touched the cornea. The corneal touch, however, did not always cause superficial keratitis. This finding may be explained by the fineness of the lashes and the tolerance of the cornea, as described by Duke-Elder.[1] Cases of epiblepharon that produce no clinical symptom require no treatment. Patients complaining of ocular pain and blurred vision should be treated appropriately.

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Epiblepharon with inverted eyelashes in Japanese children. II. Surgical repairs

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SUMMARY We used lid bracing sutures, buried sutures, and skin resection operations to correct epiblepharon in Japanese children. Epiblepharon and ocular irritation in 103 children (254 eyelids) were treated first with lid bracing sutures. Postoperatively the inversion of eyelashes resolved in 73 patients (196 eyelids). Of these 103 patients 30 (58 eyelids) developed recurrences, which included 11 who also complained of foreign body sensation and ocular pain. These 11 patients (22 eyelids) underwent a second surgical procedure (buried sutures or skin resection) before they became free of symptoms. No severe complications were noted in any of the 103 patients. We believe that lid bracing sutures correct most cases of mild epiblepharon in children and that buried sutures or skin resection are valuable for more severe conditions.

We have shown[1] that epiblepharon occurred commonly in Japanese infants but tended to disappear spontaneously with age Only 2% of high school students in our series still had the condition.[1] Although most children with epiblepharon had no or mild symptoms, some patients experiencing ocular pain needed treatment. These patients were treated initially with lid bracing sutures. If symptoms recurred, the patients underwent a second procedure, either with buried sutures or skin resection.

Subjects and methods

We selected for this study children who (1) underwent surgery for epiblepharon at Soma Municipal Hospital, Fukushima, and at Shimane Medical University Hospital, Shimane, (2) were examined at two and six months postoperatively, and (3) were followed up for a total of two years. Patients who could not be examined at one and two years were contacted by telephone. Those who underwent a second operation were observed for a minimum of two years.

An operation for epiblepharon was performed when children had an extra fold of eyelid skin, inwardly rotated eyelashes, corneal abrasion shown by staining with sodium fluorescein, and symptoms such as foreign body sensation and ocular pain. Parental agreement was obtained for all procedures. Surgery was not attempted in infants under 1 year of age

Patients were treated initially with lid bracing sutures. If the inverted eyelashes, corneal abrasion, and symptoms recurred, they were treated again with buried sutures or skin resection. Most procedures were performed under local anaesthesia. Patients younger than 6 years or those who were fearful of having surgery underwent general anaesthesia Both eyelids were treated as a rule, even in unilateral cases, to form symmetrical scars.

Simple lid bracing sutures were used to treat inferior epiblepharon. Double-armed sutures of 3-0 silk were brought from the inferior cul de sac, through the pretarsal orbicularis and out 3 mm below the eyelid margin. The arms of each suture were about 3 mm apart. Usually two sutures were placed at the medial and central portions of the lower eyelids and were tied tightly, with the beads forming a bolster to rotate the eyelashes outward. One week later the suture threads were removed.

For superior epiblepharon sutures were similarly passed from the superior cul de sac and out 3 to 4 mm above the eyelid margin. Most often three sutures were placed at the medial, central, and lateral parts of the upper eyelids. The suture threads were removed after one week.

Buried sutures were used as a second procedure. A double-armed 5-0 polyglycolic acid suture was passed in a similar way as the lid bracing suture. The conjunctival side of the entry site and the skin at the

Correspondence to Seiji Hayasaka, MD, Department of Ophthalmology, Shimane Medical University, Izumo, Shimane 693, Japan exit site were incised before suturing was performed. The sutures were tied tightly without a bolster, and buried. The wound of the skin was closed with sterilised tape. Buried sutures were not removed.

Skin resection was done in patients with large folds of eyelid skin. The semilunar-shaped fold of skin was excised, the wound was closed with 7-0 nylon, and the suture was removed after one week. To avoid ectropion postoperatively a minimal amount of skin was excised, resulting in the outward rotation of the eyelashes

Results

Of 103 children)254 eyelids) older than 2 years of age who underwent surgery with lid-bracing sutures, 73 (196 eyelids) became free of symptoms. Recurrences developed in 30 patients (58 eyelids), even though 19 had not symptoms but had inverted eyelashes touching the cornea. Only 11 complained of foreign body sensation and ocular pain (Table 1). Recurrences were distributed among patients between 2 and 18 years of age.

Both lower eyelids and upper eyelids were treated at the first operation (Table 2). About 23% of eyelids treated had recurrences. No difference in predilection for right or left eyelids was noted.

Of the 103 children 14 showed a recurrence at two months' follow-up, 30 at six months after operation (Table 3) All second operations were performed within one year of the first

Of the 11 patients who had symptoms after the first operation seven were treated with buried sutures and four underwent skin resection. All became symptom-free thereafter (Table 4). One patient who was treated with buried sutures was suspected of having an abscess two weeks postoperatively. After the sutures were removed, all signs of infection disappeared. Another patient who underwent a skin resection had a massive subcutaneous haemorrhage

Table 1 *Recurrences after first lid bracing suture procedure for epiblepharon*

Age at first operation (yr)	*Sex*	*No of patients treated*	*No of patients with recurrences**	*Percentage of recurrences*
2–3	M	1	0	0
	F	6	3	50·0
4–6	M	16	5 (1)	31 3
	F	17	6 (1)	35·3
7–9	M	12	4 (2)	33 3
	F	15	4 (1)	26 7
10–12	M	15	3 (2)	20 0
	F	11	3 (2)	27·3
13–15	M	2	0	0
	F	4	1 (1)	25 0
16–18	M	1	0	0
	F	3	1 (1)	33·3
0–18	M	47	12 (5)	25·5
	F	56	18 (6)	32·1
Total		103	30 (11)	29·1

*Recurrence was characterised by inverted eyelashes touching the cornea Numbers in parentheses indicate patients complaining of symptoms

Table 2 *Eyelids treated with lid bracing sutures (103 patients)*

Eyelid	*No. of eyelids treated at first operation*	*No of eyelids with recurrences**	*Percentage of recurrences*
Right:			
Upper	52	12	23
Lower	73	17	23
Left			
Upper	54	10	18·5
Lower	75	19	25
Total	254	58	22·8

*Recurrence characterised by inverted eyelashes touching the cornea

Table 3 *Time of recurrence after first operation*

Follow-up	*No. of patients examined*	*No of patients with recurrences**
2 mo	103	14
6 mo	103	30 (7)
1 yr	94†	30 (11)
2 yr	91‡	30 (11)

*Recurrence characterised by inverted eyelashes touching the cornea Numbers in parentheses indicate patients who underwent a second operation

†One year after first operation: nine patients reported no symptoms via telephone inquiry

‡Two years after first operation 12 patients reported no symptoms via telephone inquiry

Table 4 *Incidence of recurrences and complications*

Types of surgery	*Recurrence and complications*	*No of patients with recurrence or complication*
Simple lid bracing sutures (n=103)	None	73
	Recurrence without symptoms	19
	Recurrence with symptoms	11
	Ectropion	0
	Cosmetic problem	0
Buried sutures (n=7)	None	6
	Recurrence without syptoms	0
	Recurrence with symptoms	0
	Suspected of having abscess	1
	Cosmetic problem	0
Skin resection (n=4)	None	3
	Recurrence without symptoms	0
	Recurrence with symptoms	0
	Subcutaneous haemorrhage	1
	Ectropion	0
	Cosmetic problem	

that disappeared spontaneously after one month. Ectropion and cosmetic problems did not occur.

Discussion

The indications and methods of surgery for childhood epiblepharon are disputed, because all patients with inverted eyelashes do not have superficial keratitis, though the eyelashes touch the cornea.[1] Moreover, children with epiblepharon and superficial keratitis do not always complain of foreign body sensation or ocular pain, and the condition usually disappears spontaneously with age.[1] We therefore treated children older than 1 year who had, with epiblepharon, inwardly rotated eyelashes, superficial keratitis, and clinical symptoms.

No suture repairs were made in infants with epiblepharon who were younger than 1 year If the infants had tearing or photophobia, the involved eyelids were pulled with adhesive tape to rotate the eyelashes outwards temporarily. One child with severe epiblepharon at age 20 months was treated by lid bracing sutures but was lost to follow-up.

Children with epiblepharon and symptoms who were older than 2 years were treated surgically. Lid bracing sutures were introduced for the correction of inferior entropion by Snellen.[2] The procedure was modified by Komoto,[3] and has been widely used to treat superior and inferior epiblepharons in Japan.[4] Although this is one of the most frequent operations carried out by Japanese ophthalmologists,[4] to our knowledge no results have been previously analysed. One advantage of lid bracing sutures is that the sutures are removed, reducing the risk of infection. Most of our patients (71%) obtained good results from the procedure. Recurrence is one disadvantage of it. No complications, however, occurred in our series

The method of buried sutures used in the present study was a modification of that described by Kato[5] and by Quickert and associates.[6,7] They used chromic gut sutures and did not incise the conjunctiva. We employed polyglycolic acid threads and incised the skin and conjunctiva to bury the sutures completely. No recurrences were observed in our patients postoperatively.

Skin resection, a method proposed by Celsus,[2] may be commonly used to correct epiblepharon in Europe.[8] This procedure generally has been contraindicated for childhood cases of epiblepharon in Japan,[4,9] though Tabuchi and Yamamoto[10] recently reported good results for severe conditions. We used this procedure as a second operation to reduce large extra folds of eyelid skin. No recurrences or cases of ectropion were observed in our patients.

Patients with severe epiblepharon and epicanthus may benefit from Johnson's[11,12] V-Y plasty and skin excision. This procedure has been tried in some patients with epicanthus but was not used in the present study.

Our patients with mild epiblepharon obtained good results with lid bracing sutures. We believe that this procedure is useful in most affected Japanese children, and that buried sutures or skin resection is valuable for severe cases of epiblepharon.

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The pattern electroretinogram in glaucoma: an evaluation by relative amplitude from the Bjerrum area

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SUMMARY A new concept for evaluating the pattern electroretinogram (PERG) in glaucoma and its clinical application are described. The PERG was elicited by two different stimulus fields, namely, the whole central retinal area with a radius of 18° and the paracentral ring area between the radius of 10° and 18°. The amplitude of the PERG for each stimulus field and the ratio of them were analysed for 30 patients with glaucoma or ocular hypertension. Among these only a small number of eyes were detected as abnormal when we evaluated the amplitude itself either with the central stimulus or the paracentral ring stimulus, whereas the ratio of the two values was below normal in some cases of advanced glaucoma. We conclude that the ratio of the paracentral to central PERG is useful for detecting glaucoma.

The pattern electroretinogram (PERG) is an electrical retinal response elicited, not by the luminance change, but by the pattern stimuli in the visual field. Since the response has been considered to originate from the ganglion cell layer in the retina,[1] many studies have been reported on the PERG's clinical application to glaucoma[2-7] as well as optic nerve disorders.[8-11] However, most of the reports on the PERG and glaucoma studied only the amplitude of the PERG elicited by the central stimulus field and generally found that patients with glaucoma have statistically smaller amplitudes than do control groups.[5,6] In detecting the glaucomatous abnormality the amplitude of the PERG has not been proved to be sensitive, because it has large interindividual variation resulting in a wide overlap between glaucoma and normal control groups.

We previously reported that the PERG can be recorded from the paracentral ring area as well as from the central area. We also found that the ratio of the amplitudes from these two areas is less variable and more reliable than the amplitudes of themselves.[12] Moreover, the ratio of the paracentral to central PERG is likely to be more sensitive in detecting glaucomatous changes, since the paracentral ring corresponds to the Bjerrum area, where early glaucomatous changes are believed to occur initially.

In this report we describe an effective method of analysing the PERG in glaucomatous eyes and its usefulness in detecting abnormality.

Subjects and methods

SUBJECTS

We studied 30 eyes of 30 patients with glaucoma or ocular hypertension (OH) ranging in age from 16 to 80 years, mean 56 years. The detailed clinical findings are listed in Table 1.

In accordance with Kosaki's classification of glaucomatous field change they were divided into six groups. Stage I: Earliest stage of glaucoma without any field changes shown by kinetic Goldmann perimetry (*a*: normal field, *b*:pathological field detected only when more precise method is used) Stage II: Early stage of glaucoma with abnormal field for isoptres I-4, I-3, I-2, and I-1, but without any abnormalities for an isoptre V-4 (*a*: normal for an isoptre I-4, but abnormal for isoptres I-3, I-2, and I-1; *b*: abnormal for all I isoptres). Stage III Middle (established or developed) stage of glaucoma, with abnormal field for an isoptre V-4, but with field loss not exceeding 1/2 of the normal field for V-4 target

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Table 1 *Clinical data*

No /age/sex/eye	*Diagnosis*	*VA*	*VF*	*Full (μV)*	*Ring (μV)*	*Ring/full (%)*
1/41/F/R	OH	1 2	I	4 53	2·32	51 2
2/45/M/R	OH	1 0	I	2 73	1 35	49·5
3/34/F/R	OH	1 2	I	4·92	1 95	39 6
4/57/F/R	OH	1·0	I	3 13	1·25	39 9
5/64/F/R	SEC	1 2	I	4·76	1 87	39 3
6/66/M/R	PACG	1 2	IIa	2 50	0 93	37 2
7/41/M/R	POAG	0 7	IIa	2 95	1·37	46 4
8/55/F/R	POAG	1 2	IIa	3 59	1 64	45 7
9/52/F/L	POAG	1 2	IIb	2 31	0 82	35 5
10/80/F/L	POAG	1 0	IIb	2 22	0 82	36 9
11/16/M/L	POAG	1 2	IIb	3 00	1 15	38·3
12/70/M/L	LTG	0·9	IIb	1 63	0 56	34 4
13/69/M/R	POAG	1 0	IIIa	3·35	1 32	39 4
14/45/M/R	POAG	1 2	IIIa	4 59	2 02	44·0
15/33/M/R	POAG	1 2	IIIa	1 87	0·58	31 0
16/43/M/R	POAG	0 8	IIIa	2 89	1 17	40 5
17/66/M/L	POAG	1·2	IIIa	1 21	0 35	28·9
18/57/F/R	SEC	0 9	IIIa	1 71	0·78	45·6
19/72/F/L	LTG	0 8	IIIa	1 32	0 66	50·0
20/61/F/R	LTG	1·2	IIIa	3 84	1 62	42 2
21/76/F/R	LTG	0 7	IIIa	1 79	0 67	37 4
22/39/M/L	POAG	0 9	IIIb	2 00	0 68	34 0
23/26/M/R	POAG	0 9	IIIb	2 50	0 68	27 2
24/69/M/L	POAG	0 9	IIIb	1 07	0·33	30 8
25/70/F/R	POAG	0·6	IIIb	2 03	0 63	31 0
26/71/M/L	POAG	0 8	IIIb	2 50	0·85	34 0
27/52/M/L	SEC	1 0	IIIb	2 81	0 86	30 6
28/67/F/L	LTG	1 0	IIIb	3 28	1 17	35 7
29/77/M/L	POAG	0·3	IV	1 40	0 51	36 4
30/69/F/L	POAG	0 7	IV	1·52	0 54	35 5

OH=ocular hypertension. SEC=secondary glaucoma. PACG=primary angle closure glaucoma POAG=primary open angle glaucoma. LTG=low tension glaucoma VA=visual acuity VF=visual field, which is classified according to Kosaki's classification of glaucomatous field change.

For definitions of stages of glaucoma see text

(V-4 field) (*a*· field loss (contraction) not exceeding 1/4 of V-4 field; *b*: field loss more than 1/4 but less than 1/2 of V-4 field). Stage IV: Late stage of glaucoma, with field loss exceeding 1/2 of V-4 field but with preserved macular field (*a*: field loss exceeding 1/2 of V-4 field with preserved macular field; *b*: macular field only). Stage V. Very late stage of glaucoma without macular field but with preserved field outside the macular field. Stage VI: End stage of glaucoma with loss of V-4 field.[13]

The intraocular pressure was controlled with pilocarpine, beta-blocking agents, epinephrine, carbonic anhydrase inhibitor, or combination of them.

STIMULATION

A television monitor placed 40 cm from the subject generated the checkerboard pattern stimuli, which were reversed rectangularly with a frequency of 10 cps. Each check size subtended 48×39′ of visual angle. The mean luminance was 80 cd/m² and the contrast was 94%. Two different types of stimulus area were made available by placing one of the two masking boards in front of the TV monitor. The first allows presentation of the full pattern, that is, the checkerboard pattern inside the 18° circle The second with a central masking circle of 10° of radius provided the ring pattern (Fig. 1)

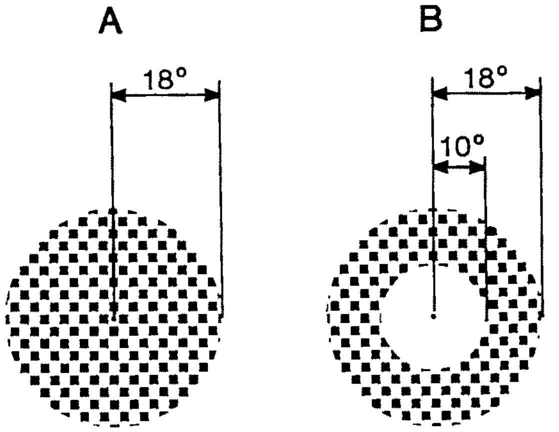

Fig. 1 *A schema of the two stimulus fields* A. *full pattern*. B. *ring pattern*.

RECORDINGS

The PERG was recorded with a corneal ERG-jet disposable electrode (Life-Tech Inc). The reference electrode was placed on the skin temporal to the test eye. The ground electrode was placed on the skin of the chin The signals were amplified with a bandpass filter setting at 0·5–30 Hz using a signal averager (MEB-5100, Nihon-Koden, Japan). We averaged 256 responses and removed artefacts from the data by an artefact rejection system.

MEASUREMENT AND ANALYSIS

Fig. 2 shows waveforms from a normal eye and from a glaucomatous eye. The amplitudes were measured from the second trough to the first peak as shown with arrows in Fig. 2. Three types of data, that is, the amplitude from 18° circle pattern (full), the amplitude from 10° to 18° ring pattern (ring), and the ratio of ring to full were analysed. For each of them the normal mean with 2 standard deviations has been reported.[12]

Results

Fig. 3a shows the distribution of the 18° pattern stimulation for eyes with glaucoma and OH, with the lower limit of the normal range. Almost all eyes in all groups had amplitudes larger than the lower limit of normal range. Fig. 3b shows the distribution of the

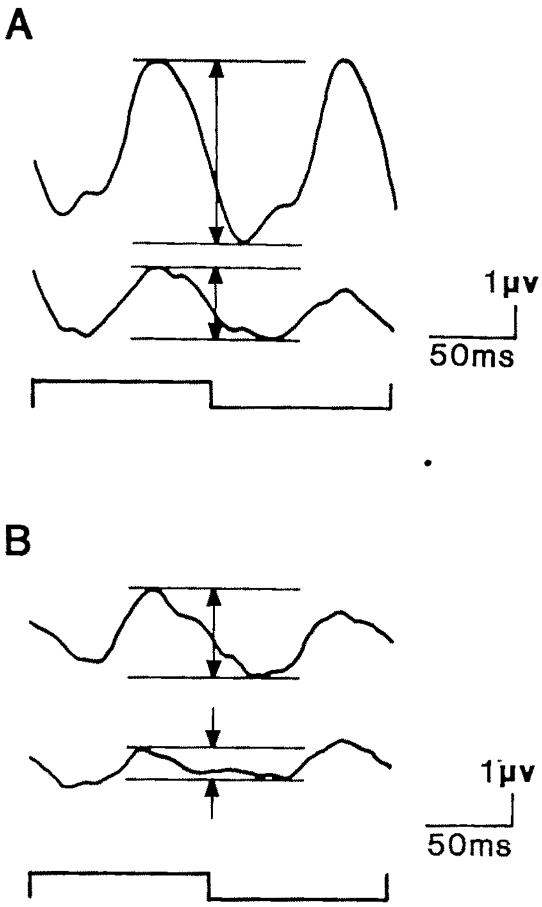

Fig 2 *Waveforms from* (A) *a normal eye and* (B) *from a glaucomatous eye. The response for the full pattern is in the upper column and that from the ring pattern is in the middle column The point of pattern change is indicated in the bottom trace*

10° to 18° ring for the same subjects. Only a small number of eyes with more advanced glaucoma were plotted under the lower limit Fig. 3c shows the distribution of the ratio of the ring to full stimulation. Eyes with fewer field defects were within the normal range, whereas a number of eyes of other groups were plotted under the lower limit. Exceptionally, most of the eyes in the classification of IIIa had a rather larger ratio. The records of their visual fields are shown in Figs. 4a–f

Discussion

A histopathological investigation has shown that glaucomatous eyes even in the subclinical stage have suffered considerable loss of ganglion cells,[14] which are the origin of the PERG. But, when we evaluate

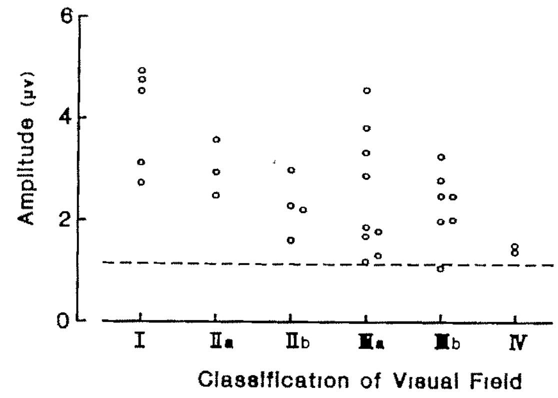

Fig. 3a

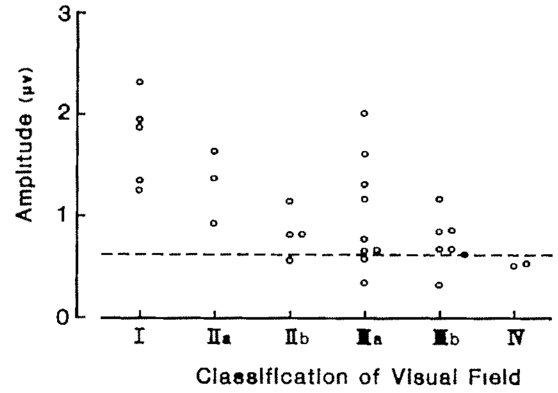

Fig. 3b

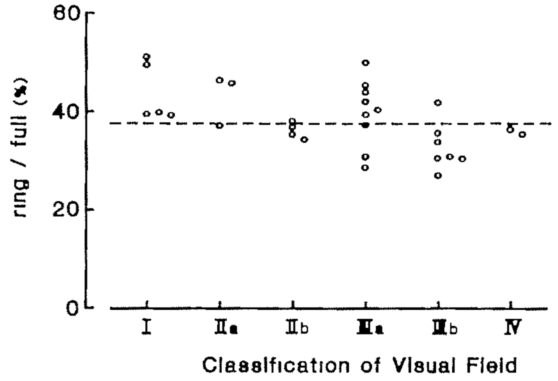

Fig. 3c

Fig. 3 *The distribution of* (a) *the amplitudes of 18° full stimulation,* (b) *the amplitudes of 10° to 18° ring stimulation, and* (c) *the ratio of ring to full among various stages of glaucomatous field change The broken line indicates the lower limit of the normal range*

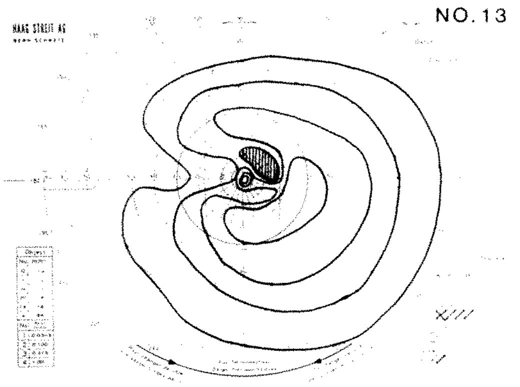

Fig. 4a

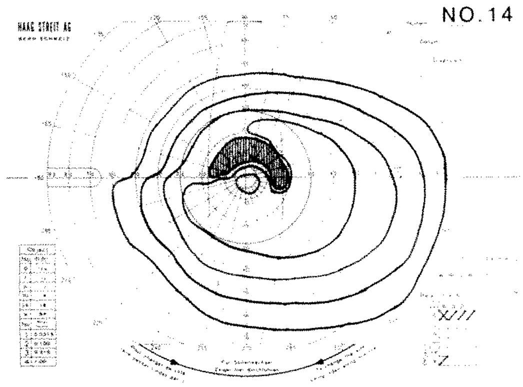

Fig. 4b

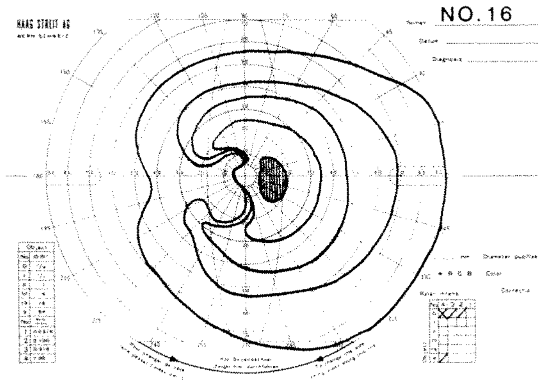

Fig. 4c

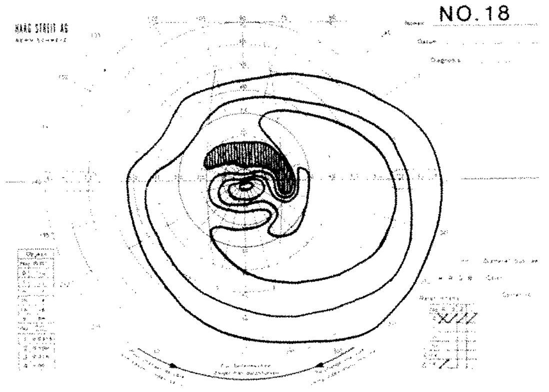

Fig. 4d

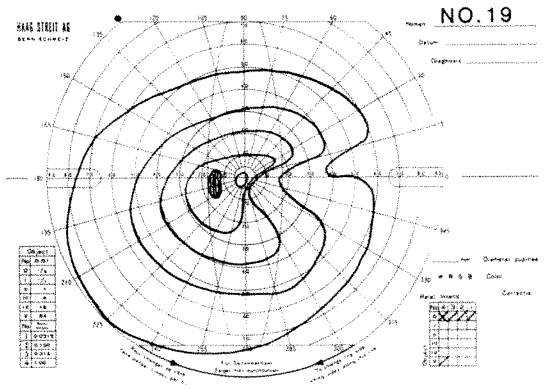

Fig. 4e

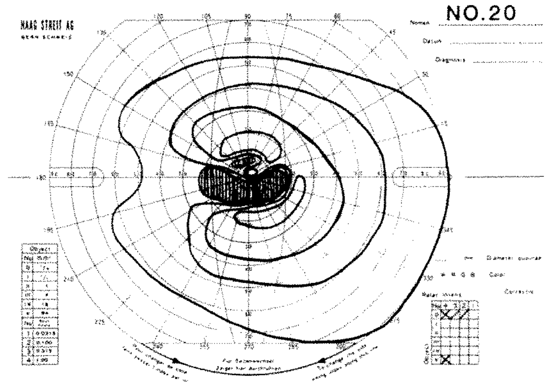

Fig. 4f

Fig. 4 *The visual fields of* (a) *case 13,* (b) *case 14,* (c) *case 16,* (d) *case 18,* (e) *case 19, and* (f) *case 20. Their ratios of ring to full were exceptionally large (Fig. 3c), which could be ascribed to the pattern of their field being hemianoptic rather than having Bjerrum defects.*

the PERG amplitude of the 18° circle, no significant abnormality could be detected in most of the glaucomatous eyes. Since the glaucomatous field defect arises in the Bjerrum region, it would be expected that in many patients a selective stimulus in this area would be more effective than that in the whole central field. From this working hypothesis we devised a ring shaped stimulus field corresponding to the Bjerrum area and found that the sensitivity of detecting the glaucomatous abnormality was slightly improved, though it was still unsatisfactory (Fig. 3b). Such insensitivity is thought to derive from the large variation in the amplitude of the PERG recorded in normal as well as in glaucomatous eyes. The variation is the result of various factors, such as pupil size, which is affected by the use of pilocarpine drops, unstable fixation, eye movement, different conductance round the eyeball, and others. But these factors have the same effects on both the amplitudes of the PERG elicited by the 18° full stimulation and 10° to 18° ring stimulation It is expected that the effects would be cancelled in the evaluation of the ratio of the two values In fact, the ratio of ring to full was shown to have a narrower normal range, with the result that most of the glaucomatous eyes with documented field change are plotted under the normal lower limit. This concept of evaluation by the ratio of two values has also been adopted in other fields of ocular electrophysiology. Examples are the L/D ratio[15] and the relative base value[16] in the electro-oculogram, and a/b ratio[17] in the electroretinogram, whose usefulness has already been established.

Some exceptional cases do exist, especially in classification IIIa (Fig. 3c). Their fields are hemianoptic rather than having Bjerrum defects (Fig. 4), and with hemianoptic field defects both responses from full and ring stimulus fields are equally reduced, resulting in a more or less normal ratio of ring to full. Additional methods to cover the cases with these rather atypical glaucomatous field defect patterns will be devised later.

On the whole, however, the ratio of ring to full has proved useful for detecting glaucomatous change in comparison with the amplitude of the PERG alone We recommend that the PERG evaluation of patients with potential glaucoma should use the ratio of Bjerrum retinal area to the overall posterior retina to achieve the most effective diagnostic results

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Effects of fusidic acid on staphylococcal keratitis

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SUMMARY We treated 20 consecutive patients suffering from staphylococcal keratitis with topical fusidic acid 1% suspension in a carbomer gel. Fifteen (79%) of the isolated *Staphylococcus epidermidis* strains were resistant to methicillin, but all were sensitive to fusidic acid by in-vitro testing. The keratitis showed evidence of healing in 17 (85%) of the 20 patients. The healing times ranged between 5 and 21 days (mean 10·5 days). In this open clinical trial fusidic acid proved to be a safe and effective antibiotic for the treatment of staphylococcal keratitis.

Bacterial infections of the cornea produce a wide spectrum of clinical signs and symptoms ranging from peripheral and superficial keratitis to central and deep corneal stromal ulcerations. Immediate initiation of specific antimicrobial therapy based on laboratory diagnosis is essential to eradicate the infectious agent and to prevent tissue damage and minimise scarring or melting.[1-3] Preservation of vision and the integrity of the ocular tissues should be the ultimate goal of therapy in any infectious disease of the cornea

Over the past two decades the use of topical steroids has increased with a corresponding increase in the risk of acquiring secondary infection by opportunistic bacteria.[4,5] Moreover widespread use of antibiotics may have contributed to the increased incidence of β-lactamase and cephalosporinase producing *Staphylococcus epidermidis*[6] in ocular infections.[7-9] There is a paucity of commercially available topical antibiotics for staphylococcal ocular infections.[10] Meanwhile, there has been an increase in strains of *Staph Epidermidis* resistant to a multiplicity of commercially available antibiotics inducing corneal infections.[11,12] There is no highly effective topical antibiotic preparation against β-lactamase-producing or methicillin-resistant staphylococci other than vancomycin. It is therefore conceded that search for effective antibacterial chemotherapeutic agents against these multiple antibiotic-resistant staphylococci and other Gram-positive cocci causing bacterial keratitis is essential in improving the visual outcome of patients suffering from bacterial keratitis.

Topical fusidic acid (Fucithalmic) has recently become available as an ophthalmic preparation. Fucidin has been used since the early 1960s for the treatment of severe systemic staphylococcal infections.[13-15] Although vast experience has been gained in the systemic use of fucidin, there are only a limited number of clinical trials on the use of Fucithalmic viscodrops in the treatment of ocular infections.[16] The main objective of this prospective open clinical trial was to assess the efficacy of 1% fusidic acid viscodrops in the treatment of bacterial keratitis caused by susceptible organisms.

Patients and methods

A total of 20 patients suffering from staphylococcal keratitis were included in this open clinical trial.

All the patients included in this study underwent an initial ophthalmological examination which included visual acuity testing, external eye examination, and biomicroscopic examination. Each patient's symptoms were recorded as well as past and current ocular treatment. Each patient had corneal scrapings which were subjected to Gram and Giemsa staining and plated on to blood agar, chocolate agar, and thioglycollate medium.[2] Treatment was begun on the basis of Gram stain interpretation. Antibiotic sensitivity testing and complete species identification were performed on each isolate. Each patient's eye was examined by two ophthalmologists, each of whom examined the patient independently and then recorded the findings before and after initiating therapy. Slit-lamp photographs were taken before and during treatment. Each patient had a routine general health examination consisting of complete

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blood cell count, urine analysis, and blood chemistry tests (blood urea nitrogen, creatinine, and fasting blood sugar levels) both before and after treatment.

Each patient was started on a regimen of topical 1% fusidic acid and examined daily for one week. After that week the patient was examined every other day for an additional week, then weekly thereafter. Scrapings were repeated on some patients during the course of treatment.

CRITERIA OF HEALING

Healing of the keratitis was defined as improvement in visual acuity, decrease in size of corneal ulcer, decrease in degree of corneal infiltration and oedema, and increased visualisation of the iris details. The size of the corneal ulcer was measured and recorded, and the degree of corneal infiltration was graded as: 3+ for severe infiltration with inability to see the iris details; 2+ for moderate infiltration where the iris details are seen but hazy; and 1+ where there was minimal infiltration with iris details clearly seen.[1] The time of observed healing, that is, re-epithelialisation of the corneal ulcer after treatment, was reported as the 'healing time' of the ulcer.

INCLUSION CRITERIA

Patients included in this study had a clinical diagnosis of active bacterial keratitis confirmed by positive smears and cultures Patients who had clinical evidence of bacterial keratitis with Gram-positive cocci in their corneal scrapings were included in the study and started on topical fusidic acid. Corneal scrapings from all patients included in the study grew *Staphylococcus spp* All the staphylococcal isolates recovered from these patients were susceptible to fusidic acid by in-vitro disc diffusion sensitivity tests However, patients with evidence of corneal perforation were excluded from this study group.

FUSIDIC ACID

The antibiotic used topically consisted of fusidic acid viscodrops (Fucithalmic) in a suspension of fusidic acid hemihydrate, expressed as anhydrous fusidic acid; the active constituent contained 10 mg per gram of the preparation (1%). The preparation, a white aqueous gel, contained benzalkonium chloride and disodium edetate as preservatives, while sodium hydroxide was used for adjustment of the pH to 5·5.

The drug was instilled in the lower conjunctival sac by the nursing staff every two hours for a total of six applications per day.

Results

There were 18 male and two female patients, with an age range of 13 to 87 years, mean 56·6 years.

Table 1 *Causative organisms and visual acuity before and after treatment with fusidic acid in patients with bacterial keratitis*

Case no	Age, sex	Vision		Healing time*	Organism
		Pre-treatment	Post-treatment		
1	76 M	HM	20/200	5	*Staphylococcus epidermidis*
2†	38 M	20/200	20/70	14	*Staphylococcus epidermidis* *Streptococcus pneumoniae*
3†	72 F	HM	HM	10	*Staphylococcus epidermidis* *Streptococcus pneumoniae*
4	15 M	20/60	20/50	12	*Staphylococcus epidermidis*
5	87 M	HM	HM	14	*Staphylococcus epidermidis*
6	73 M	HM	HM	10	*Staphylococcus epidermidis*
7	72 M	20/100	20/100	14	*Staphylococcus epidermidis*
8	21 F	CF 2·5 m	20/70	14	*Staphylococcus epidermidis*
9	50 M	CF 1 m	CF 2 m	8	*Staphylococcus aureus*
10	13 M	20/60	20/60	7	*Staphylococcus epidermidis*
11	85 M	HM	HM	5	*Staphylococcus epidermidis*
12	71 M	HM	HM	10	*Staphylococcus epidermidis*
13	74 M	HM	20/100	10	*Staphylococcus epidermidis*
14	37 M	20/200	20/100	21	*Staphylococcus epidermidis*
15†	72 F	HM	HM	10	*Staphylococcus epidermidis* *Streptococcus pneumoniae*
16	70M	LP	20/200	14	*Staphylococcus epidermidis*
17	25 M	20/100	20/50	6	*Staphylococcus epidermidis*
18	61 M	HM	20/160	10	*Staphylococcus epidermidis*
19	70 M	CF 60 cm	CF 1·5 m	12	*Staphylococcus epidermidis*
20	51 M	CF 30 cm	CF 2·5 m	5	*Staphylococcus epidermidis*

LP=light perception
HM=hand movement
CF=counting fingers.
*Days for complete re-epithelialisation after initiation of therapy
†Patients who did not respond to topical fusidic acid alone and other antibiotics had to be administered

Table 1 shows the visual acuity before and four weeks after treatment with fusidic acid 1% viscodrops. Seventeen (85%) patients improved clinically after topical therapy. Eleven (55%) of the 20 patients had improvement in visual acuity after treatment. In six patients (30%), although the ulcer healed, visual acuity did not improve. This was attributed to corneal scarring or other associated ocular disorders such as irregular astigmatism, cataract, or glaucoma. Three patients either did not respond or worsened on topical therapy with fusidic acid. Subconjunctival injections of other antibiotics such as gentamicin or cephazolin were then added to their therapeutic regimen. Repeat corneal scrapings and cultures showed no evidence of bacterial growth

HEALING OF KERATITIS

Keratitis showed evidence of healing in 17 (85%) of the 20 patients. Four patients with corneal ulcers had been unsuccessfully treated at the time of initial examination with other antibiotics, including gentamicin and chloramphenicol. These antibiotics were discontinued when the patients were entered into the study. The corneal ulcers showed complete re-epithelialisation within five days in three (15%) patients, six to 10 days in nine (45%) patients, 11 to 15 days in seven (35%) patients, and 21 days in one patient (5%). The average healing time for the corneal ulcers caused by staphylococci ranged from five to 21 days, with a mean healing time of 11·5 days.

CAUSATIVE ORGANISMS

The causative organism among 16 patients was *Staphylococcus epidermidis*. There were three cases of mixed infection with *Streptococcus pneumoniae* and *Staphylococcus epidermidis*. In one patient the organism was *Staphylococcus aureus* (Table 1). In-vitro sensitivity tests revealed that out of 19 isolates of *Staphylococcus epidermidis* 15 (79%) were resistant to methicillin, 12 (60%) to bacitracin, and 16 (80%) to erythromycin. All 19 strains of *Staphylococcus epidermidis* and one strain of *Staphylococcus aureus* were sensitive to fusidic acid. In the three patients who had mixed infection other antibiotics were added to the therapeutic regimen, such as penicillin G or cephazolin.

Discussion

The aetiology of bacterial keratitis varies from one place to another. In Saudi Arabia *Staphylococcus* species (*epidermidis* and *aureus*) are the most frequently encountered causative organisms of bacterial corneal ulcers.[9 11]

We found that topical use of fusidic acid appears to be effective in ameliorating corneal ulcers caused by antibiotic-resistant strains of staphylococci, in particular methicillin-resistant and β-lactamase producing staphylococci Fusidic acid is of unique value as there are no highly effective, commercially available, topical antibiotic preparations against many of these staphylococci

The remarkable clinical improvement of bacterial corneal ulcers caused by staphylococci following therapy with topical fusidic acid is consistent with the excellent ocular tissue penetration of fusidic acid which has been demonstrated by our group. High concentrations of fusidic acid were found in the corneal stroma and aqueous humour following topical use in the rabbit. Corneal tissue levels in the rabbit one hour after topical application of 1% fusidic acid were 10·6 mg/100 mg in intact corneal epithelium and 13·8 mg/100 mg in corneas with denuded epithelium.[17] Fusidic acid is bactericidal at concentrations close to that of the minimum inhibitory concentrations (MIC) of 0·03 to 0·16 g/l [17 18] The ability of fusidic acid to penetrate ocular tissues with intact corneal epithelium makes this antibiotic useful in the treatment of deep staphylococcal keratitis.

The incidence of multiple antibiotic-resistant strains of staphylococci is increasing, especially among patients in hospital. Recent reports have cited the effectiveness of topical vancomycin in resistant cases of blepharoconjunctivitis.[19 20] Sensitivity testing to bacitracin, a commercially available ophthalmic preparation, was not reported in the cases presented by these authors. Although vancomycin is an excellent antistaphylococcal antibiotic, we consider it should be held in reserve for strains of staphylococci resistant to other commercially available preparations. Furthermore, commercially prepared antibiotics are usually well tolerated by patients, readily available, stable, cost effective, and less likely to become contaminated from improper preparation of storage.

It is conceded that this is an open clinical trial and not a double-blind placebo-controlled clinical study. For self-evident reasons, double-blind placebo-controlled clinical trials cannot be carried out in man. Bacterial corneal ulcers must be managed early and specific antibiotics initiated promptly to prevent irreversible damage to the corneal tissue. In conclusion, the topical use of 1% fusidic acid proved safe and effective in the treatment of staphylococcal keratitis in this open clinical trial.

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Twenty cases of sympathetic ophthalmia

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SUMMARY We reviewed the charts of 20 patients with sympathetic ophthalmia who were seen in the uveitis clinic at the Eye and Ear Infirmary within an 11-year period. Of these 20 patients 14 maintained 20/50 or better visual acuity in at least one eye. We found early enucleation to be associated with a better visual prognosis, possibly due to earlier diagnosis and faster, more aggressive therapy rather than a reduction in antigenic load. The clinical appearance of Dalen-Fuchs nodules appears to indicate a more severe stage of disease. Chlorambucil was useful in patients with severe disease. To be effective and to lessen its side effects chlorambucil was given in daily dosages that were increased weekly over a short period to achieve bone marrow suppression. After a course of chlorambucil therapy intraocular inflammation could be controlled with topical steroids alone.

Sympathetic ophthalmia is a rare bilateral uveitis that can occur within a variable period of time after a penetrating injury or manipulation of the eye. We review 20 cases of sympathetic ophthalmia and contrast our clinical experience with that reported in the literature. We were specifically interested in finding out whether there were diagnostic clues for severity and whether we could elicit a better treatment regimen from previous results

Methods and materials

We reviewed the charts of patients with sympathetic ophthalmia seen in the uveitis clinic at the Illinois Eye and Ear Infirmary from 1974 to 1985. Each patient's subsequent progress was determined, whenever possible, by telephoning the referring physician. Nine patients were followed up to the present time, three patients were followed up to their death, and three patients were seen for one, three, and five years. Five patients were seen for the referral visit only. Visual acuity, onset of injury and of sympathetic ophthalmia, time of enucleation if performed, and treatment regimen were recorded. The severity of the sympathetic ophthalmia was rated as follows· the inflammation was defined as mild if it could be controlled with topical steroids or moderate if it could be managed with systemic steroids. The inflammation was considered severe if it could not be controlled with systemic steroids or if the corticosteroids could not be tapered without exacerbating the inflammation.

Fundus lesions thought to be clinically compatible with the histopathological Dalen-Fuchs nodule (granuloma) were noted. These white lesions were termed Dalen-Fuchs nodules if they were 1/10 disc diameter or less in size. The lesions had discrete hard edges and often looked like 'pin pricks' at the level of the retinal pigment epithelium (RPE). They resembled tiny hard drusen. When active, the Dalen-Fuchs nodules appear to have substance and when inactive appear as depigmented tiny spots.

For patients who had had several operations the period between the last operation and the onset of sympathetic ophthalmia was considered to be the interval between the inciting injury and the onset of symptoms Patient 16 was excluded from the analysis of intervals because the date of onset of sympathetic ophthalmia was not known.

Chlorambucil was given to patients with severe disease after they were informed of its potential side

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effects. The initial dosage was 2 mg/day orally, which was increased by 2 mg/day each week. Prednisone dosage was concurrently reduced to zero with therapeutic response or stabilisation. Platelet and white blood cell counts were monitored weekly. When the platelet count was below 100×10⁹/l and/or the white blood cell count was below 2·8×10⁹/l, chlorambucil therapy was discontinued.

Results

The 20 cases included in our study are shown in Table 1. They represented about 1·4% of the total number of referred uveitis patients seen at the Eye and Ear Infirmary. Five patients had mild disease, nine had moderate disease, and six had severe disease. Symptoms developed in seven patients within 12 weeks of the injury, in four within three to six months of the injury, and in eight more than six months after injury. Although patient 15 showed symptoms several days after the injury, this time interval could not be defined more precisely. The shortest documented time interval was four weeks and the longest 56 years. Eleven patients had additional procedures besides the original repair in the exciting eye before the onset of sympathetic ophthalmia (Table 1).

Fourteen of 20 patients maintained 20/50 or better visual acuity in at least one eye (Table 1) There was no great difference in the visual prognosis whether the patient had mild, moderate, or severe disease. Four of five patients with mild disease, six of nine patients with moderate disease, and four of six patients with severe disease maintained a visual acuity of 20/50 or better.

Nine patients underwent enucleation of the exciting eye. In five patients enucleation was performed within two weeks of the onset of symptoms (range, 4 to 11 days; mean, 6·6 days; Table 2). Four of these patients with early enucleations had final visual acuities ranging from 20/20 to 20/40, and the fifth (no. 5) had a severe cataract and 20/100 visual acuity Three of these five patients who underwent early enucleation had severe disease.

The three patients whose eyes were enucleated after two weeks from the onset of symptoms (range, 5 to 20 weeks; mean, 13·7 weeks) had visual acuities of 20/50, counting fingers, and hand motion. Two of these patients had moderate disease, and one had mild disease. An additional patient (no. 17) underwent enucleation before the onset of symptoms and had 20/200 visual acuity

Dalen-Fuchs nodules were seen in one of the six patients with mild disease, in two of nine patients with moderate disease, and in all six patients with severe disease.

We give an illustrative case report of severe sympathetic ophthalmia that was treated with chlorambucil.

CASE REPORT

On 27 August 1978 a 6-year-old white girl sustained a penetrating corneal laceration with prolapsing lens and vitreous. The wound was repaired within five hours of the injury. Following the injury the visual acuity in the right eye was hand motion. On 23 September the anterior chamber in the right eye was flat and the retina was totally detached. In the left eye an iritis with keratic precipitates, 4+ flare with fibrinous strands and 3-4+ cells with 340° of posterior synechiae were present. The left fundus was normal except for a hyperaemic disc. Because the retinal detachment was believed to be unrepairable, the right eye was enucleated on 27 September 1978. Histopathological examination showed sympathetic ophthalmia

The patient was put on a regimen of oral prednisone, 60 mg/day, for several weeks The fibrin in her anterior chamber disappeared, but 3+ flare and 3+ cells remained. On 12 October 1978 her visual acuity decreased to 20/40, and she was cushingoid. The prednisone was tapered to 80 mg every other day. On 2 November pigment clumping in the macula and several Dalen-Fuchs nodules were seen in the peripheral retina. Since the fundal lesions developed in spite of the high-dose therapy, she was initially given 2 mg of chlorambucil daily (Fig 1), as described By late December her white blood cell and platelet counts decreased to 3·5 and 90×10⁹/l respectively, and the anterior chamber inflammation subsided. At this time she was taking 10 mg of chlorambucil daily. By 4 January 1979 chlorambucil and the remaining small dose of prednisone were discontinued. The total dose of chlorambucil was 518 mg. For the next month topical steroids were used to control her inflammation and then were also discontinued. She has had no recurrence of the inflammation after seven years, and her visual acuity is 20/25.

The concurrent improvement in ocular inflammation and depression of white blood cell count occurred in patients 17, 19, and 20 also.

Discussion

According to Duke-Elder 80% of sympathetic ophthalmia cases occur within three months of the injury.[1] In our small series the incidence was 40% during that time period, possibly because we see only referred patients in our clinic. Such cases tend to be more complicated and may represent more atypical cases of sympathetic ophthalmia.

An interesting finding in our review is that the clinical presence of Dalen-Fuchs nodules appeared to

Table 1 *Clinical data of patients with sympathetic ophthalmia*

Case No	*Age at injury (yr), race, sex*	*Injury*	*Signs and symptoms of sympathetic ophthalmia (interval from last surgery to inflammation)*	*Enucleation*	*Therapy*	*Visual acuity*		*Sympathetic ophthalmia interval from onset to last observation*
						OD	*OS*	
Mild cases								
1	71 Oriental man	9/77 extracapsular cataract extraction OD with vitreous loss, intraocular steroid injection, 2 vitrectomies	16/3/79 3-week history of diminished visual acuity (2 yrs 7 mo)	29/3/79 OD	Topical steroids	E	20/50	4 yr
2	60 white man	5/78 extracapsular cataract extraction OS, severe phacoanaphylaxis, lens nucleus into posterior chamber, 6/78 vitrectomy OS	9/78 anterior chamber inflammation, Dalen-Fuchs nodules (3 mo)	—	Topical steroids ×6 mo	20/30	20/40	6 mo
3	26 white man	7/78 OD corneoscleral laceration	9/78 anterior chamber inflammation (2 mo)	—	Topical steroids	LP	20/50	1 mo
4	17 black man	6/78 OD corneal laceration; sector iridectomy several days later; 8/78 choroidal effusions drained, 4/80 penetrating keratoplasty OD	6/80 anterior chamber inflammation, depigmented areas in retina (2 mo)	—	Topical steroids	HM	20/20	5 yr
5	58 white man	9/12/81 globe perforation with retrobulbar injection OS, 11/12/81 perforation sutured, 18/12/81 vitrectomy	24/1/83 anterior chamber inflammation (13 mo)	28/1/83 OS	Topical steroids	E	20/100 (cataract)	4 yr
Moderate cases								
6	12 Hispanic boy	foreign body injury OD	2/74 2-month history pain, blurry vision (56 yr)	10/5/74 OD	Topical/systemic steroids	E	CF 1 5m	3 mo
7	38 Hispanic man	1948 struck in OD, 10/74 traumatic cataract removed	20/12/74 anterior chamber inflammation, 2-day history decreased visual acuity OS (2 mo)	26/12/74 OD	Topical/systemic steroids	E	20/20	1 yr
8	50 white man	1960 cataract extraction OD, 3 days later, extraction OS; third day after surgery, trauma OS	3-4 weeks later anterior chamber inflammation (3-4 wk)	—	Topical/systemic steroids	20/300	LP	13 yr
9	9 black boy	traumatic cataract OS; 6 months later, cataract extraction	11/82 anterior chamber inflammation, Dalen-Fuchs nodules (20 yr)	—	Topical/systemic steroids	20/20	NLP	3 yr
10	72 black man	no history of trauma; 1972 OD cataract, 1974 unrepairable retinal detachment OS	2/79 decreased visual acuity OD (7 yr)	6/79 OS	Topical/systemic steroids	HM	E	2 yr
11	28 black man	10/79 penetrating injury OS, repair delayed 2 weeks	12/79 anterior chamber and posterior inflammation (2 mo)	—	Topical/systemic steroid	20/25	20/40	*
12	9 white boy	1982 bottle rocket injury OD (no perforation noted, but eye not explored)	11/85 anterior chamber inflammation, Dalen-Fuchs nodules (3 yr)	—	Topical/systemic steroids	20/200	20/20	*
13	9 Hispanic girl	5/84 stuck OS, total hyphaema washed out, 10 days later, wound dehiscence	6/84 anterior chamber inflammation (1 mo)	—	Topical/systemic steroids	HM	20/20	1 yr
14	6 white boy	24/4/85 corneal laceration OS, flat anterior chamber	2/7/85 anterior chamber inflammation, Dalen-Fuchs nodules (3 mo)	—	Topical/systemic steroids	20/25	20/40	10 mo
Severe cases								
15	10 white boy	23/2/75 bullet wound OS	Several days later, anterior chamber inflammation, Dalen-Fuchs nodules (less than 14 days)	1/3/75 OS	Topical/systemic steroids, cyclophosphamide; chlorambucil	20/40	E	5 yr

Table 1 *Clinical data of patients with sympathetic ophthalmia—continued*

Case No	*Age at injury (yr), race, sex*	*Injury*	*Signs and symptoms of sympathetic ophthalmia (interval from last surgery to inflammation)*	*Enucleation*	*Therapy*	*Visual acuity*		*Sympathetic ophthalmia interval from onset to last observation*
						OD	*OS*	
16	36 white man	9/75 corneoscleral laceration, 3 mo later vitrectomy, scleral buckle, iridectomy; lensectomy	Date? visual acuity and fields diminished, Dalen-Fuchs nodules (unknown)	2/76 OS	Systemic steroids, chlorambucil	20/40	E	2 yr
17	13 girl from India	28/1/82 perforated globe OD	6/82 Dalen-Fuchs nodules, retinal pigment epithelial changes, subretinal neovascularisation (5 mo)	20/2/82 OD	Topical/systemic steroids, azathioprine, chlorambucil	E	20/200	4 yr
18	6 white girl	27/8/78 corneal laceration OD	23/9/78 anterior • chamber inflammation (Dalen-Fuchs nodules later during therapy) (1 mo)	27/9/78 OD	Topical/systemic steroids, chlorambucil	E	20/25	1 yr
19	56 white man	12/82 cataract extraction, 2/83, 9/83 retinal detachment repairs OD, 9/83 OD, 11/83 OS vitrectomy	7/83 vitritis, 1/84 Dalen-Fuchs nodules, bilateral subretinal neovascularisation (5 mo)	—	Topical/systemic steroids; chlorambucil	1/200	20/200	2½ yr
20	25 Hispanic woman	6/81 corneal laceration with iris prolapse	28/3/85 blurred vision; Dalen-Fuchs nodules, serous elevations of the retina (4 yr)	8-4-85 OD	Topical/systemic steroids, chlorambucil	E	20/20	1 yr

Abbreviations: OD indicates right eye, OS left eye, CF, count fingers; HM, hand motion; LP, light perception, NLP, no light perception, and E, enucleation *Seen only once at initial presentation

correlate with the severity of the disease. (See 'Materials and methods' for clinical definition of Dalen-Fuchs nodule). In our series one patient with mild disease, a few patients with moderate disease, and all the patients with severe disease had Dalen-Fuchs nodules. Histological studies support this concept Dalen-Fuchs nodules stained with monoclonal antibody to specific lymphocyte receptors show histiocytes and suppressor/cytotoxic T cells.[2] Jakobiec and coworkers suggest that these T cells might be activated cytotoxic effector T cells.[2] Some cells in the Dalen-Fuchs nodules are thought to be transformed retinal pigment epithelial cells.[3] If it is shown that Dalen-Fuchs nodules represent areas of autoimmune activity, it is not surprising that their appearance correlates with severity of disease.

Enucleation within two weeks of the onset of sympathetic ophthalmia has been associated with a better visual outcome and has been advocated by some investigators [4,5] Others believe that enucleation of an exciting eye after the onset of sympathetic ophthalmia has no effect.[6] Our data support the finding that early enucleation results in a better visual prognosis. However, patients who underwent early enucleation generally had more severe clinical disease by our criteria. Early enucleation may be associated with earlier diagnosis and quicker, more aggressive treatment We recommend that a patient with sympathetic ophthalmia who has an exciting eye with no or bare light perception should undergo enucleation, since it may offer some therapeutic benefit. Moreover, histopathological examination can confirm a clinical diagnosis. We do not advocate enucleating eyes with useful vision.

As illustrated in our case report, we have found chlorambucil dramatically to reverse the course of sympathetic ophthalmia in four patients. This subsidence of inflammation coincides with a decreased white blood cell count, after which all medications are discontinued or only topical steroids are needed to control the inflammation. The other three patients (17, 19, and 20) we treated with chlorambucil also showed this relationship.

Previous authors, using chlorambucil to treat uveitis patients unresponsive to systemic corticosteroids, did not always find this relationship between

Table 2 *Enucleation interval, disease severity, and final visual outcome**

Patient no	*Enucleation interval*	*Disease severity*	*Final visual acuity*
Enucleation less than 2 weeks			
5	4 days	Mild	20/100†
7	6 days	Moderate	20/20
15	8 days	Severe	20/40
18	4 days	Severe	20/20
20	11 days	Severe	20/20
Enucleation greater than 2 weeks			
1	5 weeks	Mild	20/50
6	3 months	Moderate	CF‡
10	4 months	Moderate	HM‡

* Patient 16 was not included owing to insufficient information. Patient 17 was not included because enucleation preceded the onset of sympathetic ophthalmia

†Patient 5 developed a cataract in this eye

‡CF=count fingers HM=hand motion

white blood cell suppression and therapeutic response.[7] This difference between the two studies may be explained by how the corticosteroids were reduced. We may have tapered the steroids more aggressively than did the other investigators. Our goal was to have the patients taking only chlorambucil. The actions of chlorambucil and prednisone could presumably be additive and induce a therapeutic response before chlorambucil caused bone marrow depression. In addition, prednisone can produce peripheral leucocytosis, which may mask a suppression of white blood cell production.

Chlorambucil immunosuppressive therapy has been associated with several major complications, but these may be averted if the total chlorambucil dose remains low. The development of normal male secondary sexual characteristics is not affected, and sperm counts remain in the normal range if the total chlorambucal dose is below 8·2 mg/kg[8] and 6·1 mg/kg,[9] respectively. Tabbara found azoospermia and oligospermia in 10 male patients with Behçet's disease treated with a total chlorambucil dose greater than 10 mg/kg [10] Recovery of spermatogenesis has been noted about three years after the discontinuation of low or high dose chlorambucil therapy.[11] Development of female secondary sexual characteristics and fertility appears to be unaffected by chlorambucil therapy.[8] [12] Chlorambucil is a teratogen,[13] [14] and its ability to damage chromosomes[15] probably means that chlorambucil is also a mutagen. However, except for one 7-year-old girl who contracted acute leukaemia after receiving a total chlorambucil dose of 300 mg (15 mg/kg)[16] acute leukaemia does not occur in patients treated with a total dose of less than 1 g.[17]

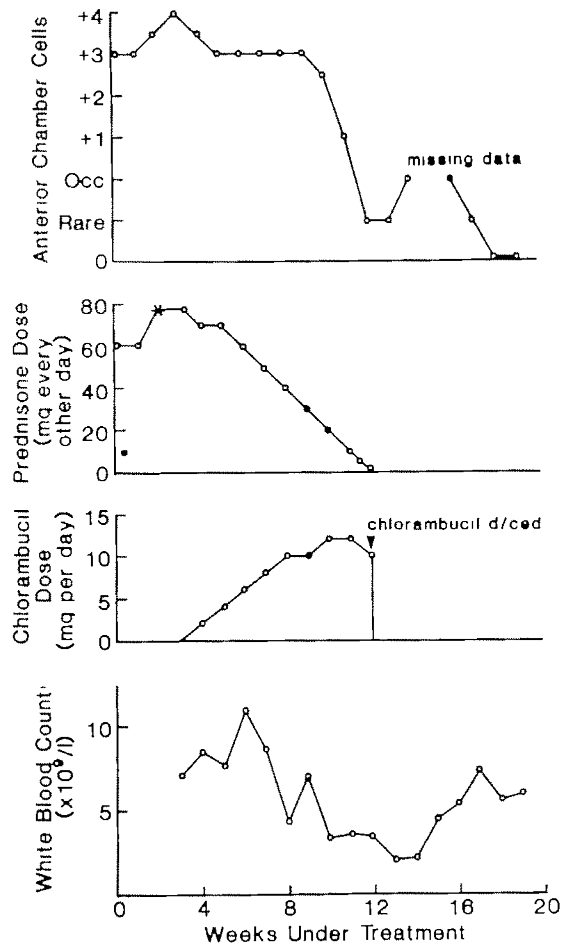

Fig 1 *The anterior chamber inflammation diminishes concurrently with the white cell suppression as a result of drug therapy in patient 18. Occ indicates occasional cell, rare, rare cell. *80 mg alternated with 20 mg daily*

Infections, particularly herpes zoster, develop in patients who tend to be on prolonged chlorambucil therapy.[18] None of our four patients had any of the complications mentioned, though evaluations of fertility were not determined

We believe that chlorambucil should be administered in progressively larger dosages. By increasing the daily dose weekly, bone marrow depression is achieved earlier, thus eliminating the ocular inflammation sooner and allowing a more rapid withdrawal of systemic steroids. This is important if the patient is experiencing severe side effects from the steroids. Moreover, a rapid induction of bone marrow depression limits the total chlorambucil dose and, as discussed, the incidence of complications from the chlorambucil therapy. However, weekly platelet and white blood cell counts are imperative. Chlorambucil immunosuppressive therapy has caused irreversible bone marrow failure.[19]

Cyclosporin, another immunosuppressive agent, has been recently used to treat uveitis.[20-23] In one study nine patients with refractory posterior uveitis were administered systemic cyclosporin. All patients had an improved visual acuity, a reduced steroid dose, and decreased inflammation. However, in seven patients cyclosporin-induced renal toxicity necessitated a reduction in the cyclosporin dose, which led to a relapse of the uveitis.[20] Others have reported that the cyclosporin dose was tapered because of nephrotoxicity and that systemic corticosteroids had to be added to suppress the inflammation.[24] This experience indicates that clinically cyclosporin suppresses but does not eradicate ocular inflammation. Thus patients with severe uveitis would need chronic cyclosporin therapy, which has been associated with renal toxicity[25] and lymphoma.[26] This is different from our experience with chlorambucil, in which only short-term therapy was required.

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^{123}I metaiodobenzylguanidine (MIBG) scintigraphy of retinoblastoma: preliminary experience

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SUMMARY ^{123}I metaiodobenzylguanidine (MIBG) is a radiopharmaceutical used for imaging neural crest tumours. The possibility of using ^{123}I MIBG for imaging retinoblastomas has been assessed in this pilot study. Ten patients were studied, nine with clinically and histologically proved retinoblastomas and one with Coats's disease. ^{123}I MIBG scintigraphy correctly identified the neoplasm in eight patients but gave a negative result in two, one of whom had Coats's disease and the other a retinoblastoma which proved to be extensively necrotic on histological examination. These preliminary results suggest that ^{123}I MIBG scintigraphy may have a role in differentiating retinoblastomas from lesions that simulate them.

Retinoblastoma is the commonest primary intraocular malignant tumour of childhood. It is a poorly differentiated neuroblastic neoplasm which may arise in any of the nucleated layers of the retina. The clinical diagnosis of retinoblastoma is rarely difficult when there is a family history of the tumour, when the ocular media are clear, and when the retina is not detached. Large tumours are more difficult to diagnose, but in bilateral cases examination of the second eye may help by demonstrating a typical early lesion. In unilateral retinoblastoma, and especially when this occurs in an older child, it may be difficult to distinguish a retinoblastoma with an exophytic growth pattern from conditions characterised by an exudative retinal detachment such as Coats's disease, and to differentiate a retinoblastoma with an endophytic growth pattern with copious vitreous seeds from inflammatory or nematode endophthalmitis.[1] A more serious though less frequent probem is failure to suspect retinoblastoma when it is present. In their analysis of 618 histologically proved cases Stafford, Yanoff, and Dornel[2] showed that almost 15% of cases had been misdiagnosed initially. The mortality rate is significantly increased by delay in enucleation of eyes with advanced tumours. It is also increased by attempts to establish the diagnosis by an intraocular biopsy procedure. This dilemma might be resolved by the development of a diagnostic imaging test which is sensitive and specific for retinoblastoma.

Table 1 *Comparison of clinical, scintigraphic, and histopathological data in patients with retinoblastomas*

Patient	*Clinical diagnosis*	*^{123}I MIBG scintigraphy*	*^{99m}Tc-MDP scintigraphy*	*Histology*	
				Grimelius staining	*Tumour necrosis*
1	Retinoblastoma	++ve	−ve	−ve	II
2	Retinoblastoma	++ve	−ve	−ve	I
3	Retinoblastoma	+ve	−ve	−ve	I
4	Retinoblastoma	++ve	−ve	−ve	I
5	Retinoblastoma	+ve	−ve	−ve	II
6	Retinoblastoma	++ve	+ve	NP	NP
7	Retinoblastoma	−ve	−ve	−ve	III
8	Coats's disease	−ve	−ve	−ve	–
9	Ectopic intracranial retinoblastoma	++ve	−ve	NP	NP
10	Ectopic intracranial retinoblastoma	+ve	−ve	NP	NP

NP=not performed
MIBG=metaiodobenzylguanidine
MDP=methylene diphosphonate.
−ve=grade 0 (no uptake)
+ve=grade 1 (minimal uptake).
++ve=grade 2 (intense uptake)
Grade I=tumour mostly viable with little necrosis
Grade II=much viable and necrotic tissue
Grade III=tumour mostly necrotic with little viable tissue

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Radioactive tracers like ^{32}P[3] and ^{131}I chloroquine[4] have been used for localising these tumours, with variable results. In the last decade radioiodinated metaiodobenzylguanidine (MIBG) has been used extensively to image phaeochromocytomas, paragangliomas,[5] neuroblastomas,[6,7] carcinoids,[8] and other neural crest tumours containing cytoplasmic neurosecretory granules.[9] MIBG is an analogue of guanethedine and shares many cellular transport properties with noradrenaline. It is transported across the cell membrane via the neuronal uptake-one system which is an active process and is dependent on the sodium pump[10] and by a sodium-dependent pathway which is probably passive diffusion.[11] From the cell cytoplasm MIBG is transported across the granular membrane of the neurosecretory granules via a proton pump[12] and stored in the neurosecretory granules.[13] Since retinoblastomas are of neural origin,[14] we postulated that these tumour cells would share the metabolic pathway of specific MIBG uptake and storage with other neural tumours and could thus be imaged The study was undertaken to evaluate this hypothesis.

Materials and methods

PATIENTS

Ten patients, aged 6–48 months, were included in this study. Five patients had a known primary retinoblastoma, three had a doubtful clinical diagnosis of retinoblastoma, and two patients had bilateral disease with ectopic intracranial retinoblastoma (EIR) (Table 1). In the two patients with EIR the ocular tumours were treated by external beam radiotherapy, and at the time of imaging there was no evidence of active ocular disease. Each patient underwent extensive ophthalmological and systemic examination to evaluate the stage of the disease. ^{99m}Tc-methylene diphosphonate (MDP) radionuclide bone imaging was carried out as part of the routine staging procedure in each case. In eight patients enucleation of the involved eye was undertaken.

IMAGING PROTOCOL

Prior to injection of ^{123}I MIBG a drug history was taken to rule out the possible use of drugs which interfere with tracer uptake.[5] Each patient received 400 mg of potassium perchlorate to block the uptake of free iodine by the thyroid. Between 74 and 185 MBq (2–5 mCi) of ^{123}I MIBG (Amersham International PLC) was given intravenously over a period of 20–30 seconds with the patient lying supine. Images were obtained with a large field of view gamma camera (Siemens ZLC) with a high-resolution low-energy collimator and an on-line computer (PDP 11/34). The patient was placed supine with the head fixed in a foam head support, and static images of 400 000 counts each were obtained for the skull in the anterior Waters view, anterior chest, anterior abdomen, posterior chest, and posterior abdomen at 4 h and 24 h after injection. Additional oblique and lateral images were obtained when needed. In all subjects mild sedation was required for the 24 h study to avoid patient movement, since obtaining each image took approximately 20–30 minutes, and movement of the head during this time interval would have degraded the image.

^{99m}Tc-MDP bone scanning was carried out 72–96 h after ^{123}I MIBG study in each case. Approximately 20 MBq/kg body weight of ^{99m}Tc-MDP was injected intravenously, and static images were obtained three hours after the injection, as in the ^{123}I MIBG study.

HISTOLOGICAL TECHNIQUE

The enucleated eye was immediately fixed in 10% formalin. The formalin fixed tissue was routinely embedded in paraffin wax, and sectioned at 4 μm Sections were all stained with haematoxylin and eosin and for the purposes of this study by the argyrophil Grimelius method.[15] The sections were examined by light microscopy. The numbers of viable cells in the tumour sections were scored on a scale of I–III· I=tumour mostly viable, with little necrosis; II=much viable and necrotic tissue; III=tumour mostly necrotic, with little viable tissue. Assessment of all tissue sections was carried out without prior knowledge of the ^{123}I MIBG scintigraphy results by an experienced pathologist (DAL).

DATA ANALYSIS

Image processing of the 4 h and 24 h digitised computer images was carried out by the unsharp masking technique.[16] This technique helps to increase the detection of abnormalities by improving the signal to noise ratio. The digitised computer images (colour scale, unprocessed and processed) were analysed by four observers as a blind control study (JB, JLH, JEK, KEB). The images were classified with respect to their ^{123}I MIBG uptake intensity in the orbital region on the anterior view of the skull at 24 h into the following three groups: grade 0 no persistent uptake; grade 1 minimal, persistent, discernible uptake; grade 2 intense, persistent uptake (less than or equal to that in the adjacent salivary glands). The criteria for normal and abnormal distribution of the tracer in other organs were the same as described previously.[17]

Results

Of the 10 patients imaged ^{123}I MIBG scintigraphy was

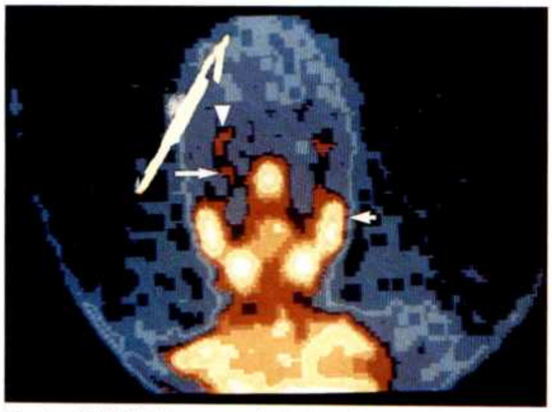

Fig. 1 ^{123}*I MIBG processed scintigraphic image 24 h after injection (case 1). Arrow head indicates uptake by the lacrimal gland, large arrow indicates uptake by the tumour, small arrow indicates uptake by the salivary gland.*

positive in eight. Six of the eight positive patients proved to have a large retinoblastoma in one eye. ^{123}I MIBG scintigraphy correctly showed uptake in all six cases (Figs. 1, 2). The two remaining patients with positive results had previously treated bilateral ocular tumours, and currently had ectopic intracranial retinoblastoma. One of the two had both eyes removed for retinoblastoma and the other had been treated successfully with radiotherapy for tumour in both eyes. In these cases MIBG scintigraphy correctly identified the intracranial retinoblastoma (Fig. 3) but showed no orbital uptake. In two of the 10 patients scintigraphy was negative: one had a retinoblastoma and the second had Coats's disease.

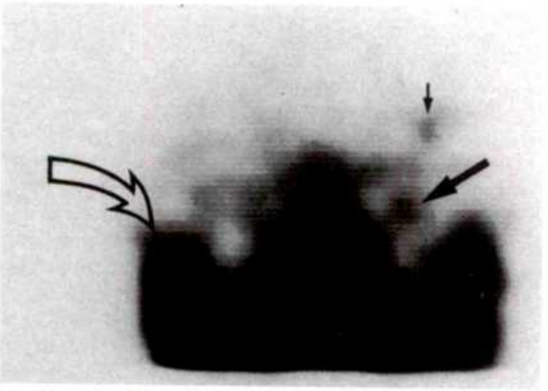

Fig. 2 ^{123}*I MIBG processed scintigraphic image 24 h after injection (case 5). Magnification ×2. Small arrow indicates lacrimal gland uptake on the right side; the left lacrimal gland was not visualised in this case. Larger arrow indicates uptake in the left orbital region. Open arrow indicates normal salivary gland uptake.*

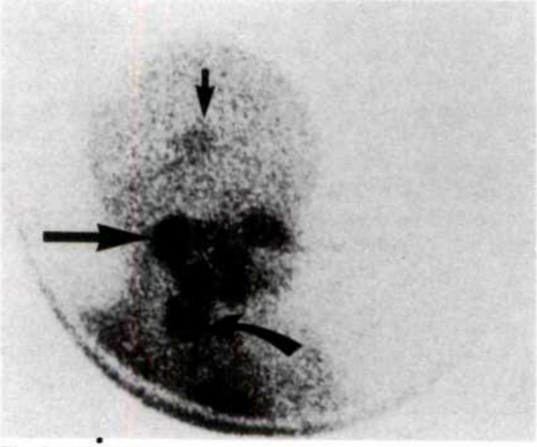

Fig. 3 ^{123}*I MIBG unprocessed scintigraphic image 24 h after injection. Left lateral view of the skull (case 9). Small arrow indicates uptake by the tumour in the pineal region. Large arrow indicates uptake by the salivary glands. Curved arrow indicates uptake by the thyroid gland due to incomplete blockage.*

Normal bilateral uptake of ^{123}I MIBG was observed in the lacrimal glands of most patients (Fig. 1), except cases 3 and 5 (Fig. 2), where only one gland was visualised; no explanation could be found for this discrepancy. In cases 9 and 10 the lacrimal glands were not visualised owing to prior therapy for the orbital tumour in these two cases. The uptake was more prominent in the 4 h images than in the 24 h images. Distribution of the tracer in other organs was within normal limits.[17]

In three cases (1, 2, and 4) the activity was measured in the enucleated eye. The calculated activity, expressed as a percentage of the injected dose at 48 h, was 0·001%, 0·002%, and 0·007% respectively. Also at 48 h the ratio of activity in the enucleated eye to that in the same weight of blood drawn during removal of the globe was 1·29, 1·57, and 1·98 respectively.

On analysis of the images there was good agreement among the four observers in detecting the lesion with a mean value of 90% sensitivity. Of the 20 images analysed disagreement occurred on two unprocessed images in two subjects (3 and 5). All observers labelled these as negative, but called them positive on the corresponding processed images (Table 1). The overall sensitivity of ^{123}I MIBG for tumour detection was 90% and specificity was 100% in this limited series. ^{99m}Tc-MDP bone scan images showed normal distribution of the tracer in all patients except case 6, where uptake was seen in the left orbital region (Table 1).

Eight patients underwent enucleation. In seven of these eight patients histological sections showed the tumours to be composed of sheets of small, densely packed, round cells with focal rosette formation and various degrees of necrosis and calcification. In some cases the bulk of the tumour was necrotic while in other cases there was relatively little necrosis. In one case (case 8) the findings were typical of Coats's disease, with exudative changes and cholesterol crystals present in the section. Grimelius staining was consistently negative on all cases (Table 1).

Discussion

This study has shown that retinoblastoma can be imaged with ^{123}I MIBG. Uptake of ^{123}I MIBG by the tumour shows a wide spectrum from no detectable activity to high tracer uptake. Overall uptake by retinoblastoma was low compared with other neural crest tumours.[5 9 18] The uptake of ^{123}I MIBG by the tumour appears to be specific, since a non-specific agent like ^{99m}Tc-MDP showed no uptake in the orbital region in any patient except case 6, where uptake was seen. This was attributed to the dense calcification in necrotic tumour cells.

The absence of neurosecretory granules, as reflected by the negative Grimelius staining of tissue sections, may imply that the storage system for ^{123}I MIBG in these tumours is absent or deficient but the uptake mechanism remains functional. This is in keeping with the finding that the degree of tracer uptake was related to the proportion of viable cells in the tumour sections as seen in cases 2, 3, and 4. In cases where the tumour was extensively necrotic there was either no or poor uptake. Mechanisms for uptake of ^{123}I MIBG by these tumour cells are probably a combination of an active process (uptake-one system)[10 11]; sodium-independent pathway which is probably passive diffusion of the tracer across the tumour cell membrane and retention in the cytoplasm[10 11]; and breakdown of the blood-retinal barrier in case of retinoblastomas and/or blood-brain barrier in case of EIR, facilitating the entry of the tracer.

Previous radiotherapy or chemotherapy also reduced tracer uptake. This was seen in case 9, where the ocular tumours had been treated with radiotherapy and showed no uptake while the EIR showed good uptake. In the case of patient 10 radiotherapy for the ocular tumours and chemotherapy for EIR was also given. There was no uptake by the ocular tumours, and uptake by the EIR was low. This is in keeping with the findings of other investigators in the context of other neural crest tumours.[6 8 18]

Some of the practical problems experienced during this study and the precautions needed to avoid them require mentioning Since the overall tumour size was small, with low tracer uptake, and as the tumour was surrounded by spatially inhomogeneous high background activity in the salivary glands and the nasopharangeal region, proper camera positioning was important to get a clear delineation of the orbit from the adjacent activity. Patient movement was another limiting factor, especially in the 24 h study, since obtaining each image took approximately 25–30 minutes, and even a slight amount of head movement caused deterioration in the quality of the image. In small infants head movement occurred in spite of mild sedation and restriction by a foam head support. These problems can be solved if a high tumour to background ratio can be achieved. In this context the possibility of improving tumour uptake by means of other radiopharmaceuticals such as radiolabelled monoclonal antibodies is being explored.[19 20]

In this limited series the sensitivity and specificity of MIBG in imaging retinoblastomas was high, but a larger series would be required to define its precise clinical role. It is hoped that ^{123}I MIBG may ultimately provide a simple, non-invasive technique for screening the whole patient for metastatic retinoblastoma in a single procedure. MIBG may also have a role in the assessment of disease response in patients following radiotherapy. This would require that treatment be shown not only to reduce ^{123}I MIBG uptake but also to correlate with the objective evidence of tumour shrinkage, cell necrosis, or extirpation of tumour tissue.

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Slow-release artificial tear inserts in the treatment of dry eyes in patients with rheumatoid arthritis

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SUMMARY Twenty-two patients with rheumatoid arthritis and moderate to severe bilateral keratoconjunctivitis sicca were treated with artificial tears and a soluble slow-release artificial tear insert in a crossover trial. While using the inserts all but two patients reported an improvement in their symptoms. All the patients showed an improvement in the degree of conjunctival and corneal staining while using the inserts (p=0·0001 and 0·00001 respectively). Nineteen patients (86%) found the inserts an acceptable form of therapy and 14 (64%) preferred them to other treatment regimens. Placement of the insert was not a problem despite all the patients having rheumatoid changes in their hands resulting in varying degrees of deformity. Two patients experienced initial difficulties with placement, but these were quickly resolved.

The treatment of patients with keratoconjunctivitis sicca (KCS) remains a problem. Various types of treatment are used to augment tear function. Occlusion of the puncta helps to prevent drainage of tears, but usually supplementation with artificial tears is necessary. Numerous preparations are available, and by trial and error the one most suitable for a given patient can be found. The most popular preparations are based on methylcellulose or polyvinyl alcohol, and act by replacing the aqueous component of tears and by helping to stabilise the tear film. The disadvantage of this mode of therapy is that it is short lived and drops must be instilled regularly, especially in severely affected patients. No study has satisfactorily shown that the solutions remain in contact with the cornea for more than 15 minutes after instillation.[1,2] This problem becomes significant in patients with rheumatoid arthritis (RA) in whom manual dexterity is reduced. KCS is common in these patients, the usual reported incidence being between 15 and 25%,[3,4] but higher rates have been found.[5] In a study of 104 RA patients in this hospital[6] 22 patients (21·2%) were found to have evidence of KCS as shown by ocular symptoms and corneal or conjunctival staining, together with a reduced tear break-up time (BUT), reduced No. 1 Schirmer test, or poor marginal tear strip.

A number of workers have investigated the use of various types of slow-release artificial tears (SRAT). The inserts were found to increase BUT and to stabilise the tear film, both in animals[7] and in normal human volunteers.[8,9] SRAT have been reported to be beneficial in patients with KCS[10-14] and in dry eyes secondary to the practolol syndrome.[15] In these studies there was an improvement in both subjective symptoms and in the objective evaluation of corneal and conjunctival staining with rose Bengal Two problems encountered were expulsion of the insert and blurring of vision resulting from the thickened precorneal tear film. These problems were overcome to a great extent by making the inserts smaller.[9,11,12] A commercially available rod shaped SRAT insert is now available and is supplied individually packeted (Merck Sharp and Dohme). The insert is composed of preservative-free hydroxypropyl cellulose, weighs 5 mg, and measures approximately 3×1 mm. One insert is placed into the inferior conjunctival fornix each morning by means of a soft flexible applicator. Fluid is imbibed, possibly from the conjunctival tissue,[13] and the insert swells to form a small soft mass. The hydroxypropyl cellulose is released continuously into the tear film. One insert usually lasts all day; it completely dissolves and does not require removal. The absence of preservatives in the inserts may be an added advantage, as many of these substances are reported to cause irritation and instability of the tear film.[12]

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The use of SRAT would be ideal for patients who, because of deformity or the necessity of frequent instillation of drops, find it difficult to keep their eyes adequately moist. However, placement of the insert requires a certain degree of manual dexterity. Difficulty in placing the insert may therefore prevent older patients and those with RA and hand deformity from using this form of therapy. Little mention has been made of this problem in previous studies, but Katz *et al.*[11] reported that one patient with severe RA and one with bilateral aphakia dropped out of their trial because of difficulty with insertion. Other studies of SRAT in patients with KCS have included patients in whom the disorder had a wide range in severity and various causes.

This paper reviews a group of RA patients with varying degrees of hand deformity and moderate to severe KCS, who received methylcellulose drops and SRAT inserts in a crossover trial.

Patients and methods

Twenty-two patients (19 females and 3 males) with RA and bilateral KCS were recruited into the study. Their average age was 50·7 years (range 39 to 66 years), and the mean duration of KCS symptoms was 5·6 years (range 23 months to 19 years). All were using artificial tears frequently, and most had been referred from the arthritis clinic in this hospital for ophthalmological assessment. A full eye examination was performed and a patient was admitted into the study if all the following criteria were fulfilled in both eyes: symptoms of KCS despite the use of artificial tears; a Schirmer's test (without anaesthesia) of 5 mm or less; a BUT of 10 seconds or less; corneal staining with 1% rose Bengal stain.

An attempt was made to assess the effect of SRAT on the patients' symptoms and on the degree of epithelial damage as indicated by staining. These two criteria were thought to represent the most important subjective and objective criteria respectively in KCS

At the initial examination patients were questioned about their symptoms and asked to grade them as absent, mild, moderate, or severe These were scored 0, 1, 2, or 3 respectively. The conjunctiva and cornea were stained with 1% rose Bengal by applying a microdrop to the superior bulbar conjunctiva. The amount of staining was assessed as absent, mild, moderate, or severe and scored 0, 1, 2, or 3 respectively. The initial examination was performed while the patients were using their regular tear replacement therapy.

Certain criteria excluded patients from this study. These were: any ocular infection, trauma, or surgery within the preceding three months; the use of contact lenses; the presence of other ocular diseases except lens opacities; or the use of any ocular medication except tear replacements.

The patients were allocated randomly according to a computer-generated random numbers table into two groups. The first group used a single soluble insert each morning. This was placed into the inferior conjunctival fornix with a flexible applicator. The second group used methylcellulose artificial tears, 2 drops four times a day. After two weeks the patients were reassessed, and both groups then used artificial tears for a week. The original treatment was then switched so that group 2 used the insert daily for two weeks and group 1 continued on artificial tears.

At the end of each trial period the patients were fully examined and their symptoms and staining were graded as described above. On completion of the period on the inserts the patients were asked about any difficulties in placing the insert and whether it was stable or extruded. At the end of the study the patients were asked whether they preferred using drops or the inserts.

Results

All 22 patients had RA with varying degrees of hand deformity and loss of dexterity. Two patients had initial difficulty in placing the inserts into the lower fornix but overcame the problem after a few attempts. Six patients experienced some difficulty in retaining the inserts, but in four this did not persist. The two remaining patients lost their inserts in the afternoon and continued with drops until another insert was used the next morning. In total, eight patients (36%) experienced some difficulty in using the insert, either with placement or retention, but this persisted in only two patients (9%). No serious side effects were encountered during the trial.

The median scores of the patient's symptoms on both the insert and the drops are shown in Table 1. Significance was calculated by the Wilcoxon test with Bonferonni correction. Because the eyes of a patient

Table 1 *Median scores of symptoms: left eye (22 eyes)*

Symptom	*Drops (semi-IQR)*	*Inserts (semi-IQR)*	*Significance (p) left eye (right eye)*
Burning	1·23 (0·595)	0·15 (0·324)	0·0005 (0·0002)
Tearing	0·23 (0·467)	0·72 (0·611)	0·12* (0·31)*
Dryness	1·28 (0·667)	0·08 (0·289)	0·0005 (0·0002)
Itching	0·94 (0·690)	0·15 (0·324)	0·0013 (0·0005)
Photophobia	0·15 (0·324)	0·08 (0·289)	0·39* (0·39)*
Soreness	0·83 (0·628)	0·15 (0·324)	0·0043 (0·003)
Blurring	0·02 (0·261)	0·02 (0·261)	(*)
Foreign body	1·1 (0·367)	0·19 (0·370)	0·0003 (0·00001)

*Not significant.

Semi-IQR = semi-interquartile range (or quartile deviation)

Table 2 *Median scores or rose Bengal staining. left eye (22 eyes)*

	Drops (semi-IQR)	*Inserts (semi-IQR)*	*Significance (p) left eye (right eye)*
Conjunctiva	1·23 (0·858)	0·11 (0·306)	0·0001 (0·00001)
Cornea	1·27 (0·869)	0·15 (0·324)	0·00001 (0·00001)

Semi-IQR see footnote to Table 1.

cannot be considered independent,[14] only the results for each patient's left eye are given (n=22). The results for the right eyes were similar, but only the significance levels are tabulated. There was a significant improvement in burning, dryness, itching, soreness, and foreign body sensation while they were using the inserts. The degree of blurring was the same with both types of treatment. There was a small increase in tearing and decrease in photophobia. Neither change was statistically significant. All but two patients reported improvements in their symptoms while using the inserts.

Table 2 shows the median scores for conjunctival and corneal staining. There was a significant improvement in these signs while the patients were using the inserts, and all patients improved on this therapy.

At the end of the trial the patients were asked which form of therapy they preferred. Fourteen (64%) preferred the insert; these included two patients who had had initial problems in retaining the insert. Eight patients preferred drops as their main form of therapy, though five stated a wish to have SRAT inserts for intermittent use. The main reasons given for preferring drops were the difficulty in placing the insert (three patients), less blurring with drops (three patients), and the cooling effect of drops (six patients). The degree of hand deformity had no correlation with the type of therapy preferred. Four patients with gross hand deformity were among the most enthusiastic supporters of the insert, whereas two patients with mild hand deformity experienced difficulty in placement.

Discussion

Slow-release delivery units for ocular medication have not met with much success. Problems with extrusion and discomfort have been encountered, and most attempts have been abandoned. Unnoticed loss of an antiglaucoma system can have serious consequences, and inspection of the fornices can itself precipitate extrusion of the unit. SRAT are designed to alleviate symptoms of KCS, and loss of the insert will result in recurrence of symptoms, thus alerting the patient to the loss. Only two patients (9%) in this study had persistent problems with extrusion of the inserts; this usually occurred during the afternoon after many hours of useful therapy. Loss of the insert was obvious to the patient, but in cases of doubt the insert can be palpated through the skin of the lower lid and felt to be present in the lower fornix.

To become a useful treatment SRAT inserts must be easy to use by the patients they are designed to help. Placement of the inserts is a potential problem that could limit this type of therapy to certain groups of patients. RA patients with secondary hand deformities would be expected to highlight this difficulty. However, few problems of this nature were found in this study. Only two patients experienced initial difficulty in placement and both overcame the problem. Both these patients had minimal hand deformities.

Our experience with normal controls has shown that inserts are poorly tolerated and are soon expelled. This is not the case in patients with KCS, who, because of their symptoms, seem better able to tolerate a foreign body in their fornices. This tolerance is reinforced by the improvement in symptoms that occurs with the insert in situ. Only two patients considered their overall symptoms worsened while on SRAT. As in other studies, a significant improvement in most symptom scores was reported by our patients. Unlike other studies, however, a problem with blurring while on SRAT was not found, and although a higher median score for tearing while on SRAT was recorded this was not significant. Other studies[10-12] that reported decreased vision with the inserts did not make corneal staining with rose Bengal a criterion for inclusion into their study. It is possible that in this study any deleterious effect on vision from the insert was masked by the improvement in the integrity of the corneal epithelium and subsequent improvement in the visual acuity. All patients showed improvement of conjunctival and corneal staining while on the SRAT; the changes in the median scores were highly significant.

Fourteen (64%) of the patients stated a preference for SRAT and a further five requested them for intermittent use. Thus a total of 19 patients (86%) indicated some degree of approval for this form of therapy. Many patients wished to use drops if they felt a need, the usual reason given being their 'cooling effect'. Subsequent follow-up has not revealed any problems arising from this dual therapy; in particular the insert does not seem to be more prone to expulsion. Other studies[10,11,14] reported a very similar percentage of patients who preferred SRAT as the main form of therapy, though in the study by Katz *et al.*[12] 75% of their patients preferred inserts. The similar preference rate in this study indicates that no serious or specific problems were encountered in the use of SRAT inserts by RA patients.

In conclusion, this study demonstrates the usefulness of SRAT in the management of KCS. Placement of the insert has been cited as a problem of this form of therapy. However, this was not borne out by the RA patients in this study Decreased manual dexterity is therefore not a contraindication to attempting a short trial of SRAT in a patient who is experiencing difficulty in keeping the eyes adequately moist with artificial tears.

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Naturally occurring antibodies to bovine and human retinal S antigen: a comparison between uveitis patients and healthy volunteers

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SUMMARY The antibody responses to human and bovine retinal S antigen in the sera of patients with uveitis from various causes were compared with those of a group of healthy volunteers who were fully screened for signs of eye disease. Antiretinal antibodies were found with equal frequency and through the same range of titres in patients and controls, irrespective of the nature or activity of the uveitis. These findings were confirmed by spectrotypic analysis of sera from patients and controls where the predominant serum antibody response was polyclonal. In a small group of patients with retinal vasculitis there was an additional monoclonal response, indicating clonal expansion of a single lymphocyte subset. The prevalence of serum antibodies to retinal antigens in the normal population may indicate a protective role for 'natural' autoantibodies, as has recently been suggested for autoimmune diseases generally.

Autoimmunity to retinal antigens, particularly retinal S antigen,[1 2] has been implicated in the pathogenesis of idiopathic uveitis. Gregerson, Abrahams, and Thirkill[3] reported that antibodies to S antigen and to retinal cell membrane proteins (P antigen) occurred in patients with various forms of uveitis, though antibody levels bore no direct correlation with phasic activity of the disease.[4 5] Using an immunoblotting procedure, this group also found patients with uveitis had serum antibodies to several soluble retinal proteins, including a 40 K and a 33 K protein, as well as S antigen (50–55 K[6 7]). Dumonde *et al.*[8] used an immunofluorescent antibody technique to show that patients with retinal vasculitis had raised antibody titres to retinal S antigen and that there was an inverse correlation between the level of circulating immune complexes and severity of disease. They suggested that immune complexes, possibly involving anti-S antibodies, serve a protective immunomodulatory role via the idiotype network.

The lack of correlation between autoantibody titres and disease activity in uveitis has raised questions on their relevance to the disease. Antibodies to various self-antigens occur widely in the normal population, and Murray[9] has recently shown that, contrary to previous reports, there is no difference in the titres of non-organ-specific autoantibodies in patients with uveitis compared with normals. In fact, B and T cell autoreactivity is considered by some to be the normal state, and indeed is a sine qua non for antigen recognition via the major histocompatibility complex (MHC) system.[10] The degree of autoreactivity, however, is held in check by a variety of controlling (suppressor) mechanisms. Autoimmune disease (AID) may therefore be the result of an imbalance in this state—that is, it is the degree of autoreactivity which determines whether the organism is adversely affected (for review see Smith and Steinberg[11]). This suggests that autoantibodies found in both normal people and patients may simply represent an epiphenomenon, which might occur, for example, as a result of polyclonal B cell activation during bacterial or viral infection. In contrast, if clonal restriction of antibody secretion occurred in certain disease states, then this might indirectly support the view that they were aetiologically important either in the initiation or in the perpetuation of the disease. Mono- or oligoclonal restriction of autoantibody against defined antigens (the acetylcholine receptor, IgG, thyroglobulin, DNA) has been reported in human and experimental

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models of autoimmune disease,[12-14] including S-antigen-induced uveitis in guinea-pigs.[15]

In this report we present data on secretion of antibody to retinal S antigen in patients with various forms of uveitis, including chronic idiopathic uveitis affecting the posterior segment of the eye, and compare the results to antiretinal antibody titres in a group of normal controls who were screened for evidence of subclinical retinal or uveal disease. In addition we have studied the antibody spectrotype of antiretinal antibodies by reverse immunoblotting.[13] Our results indicate that there is no difference in the occurrence of antiretinal S antigen antibodies between uveitis patients and normal controls, and that high levels of anti-S antibody can occur in apparently healthy people as well as uveitis patients. Spectrotype analysis indicates that in most people (patients and controls) antibody secretion is polyclonal. However, monoclonal antibodies were observed in two patients both of whom had retinal vasculitis as part of their chronic intraocular inflammatory disease.[16]

Materials and methods

Patients. Patients with various forms of uveitis and uveoretinal inflammation who presented to the Uveoretina Clinic, Aberdeen Royal Infirmary, were initially classified by diagnosis (see Table 1) and severity of disease. As part of their examination for uveitis 10 ml of whole blood were collected from each patient, and the serum was separated and stored at −20°C before use. Twenty-four healthy volunteers of similar age range and sex distribution who were free of uveoretinal disease (active or past inflammation) as determined by slit-lamp biomicroscopy and dilated indirect ophthalmoscopy were accepted into the study as controls.

Preparation of retinal S antigen. Bovine retinal S antigen was prepared by the method of Al-Mahdawi *et al.*[6] with minor modifications. Human and guinea-pig S antigens were prepared by similar techniques and also by high-performance liquid chromatography with a TSK-DEAE column. The purified antigen migrated as a single band after SDS-polyacrylamide gel electrophoresis. Protein concentration was measured by a dye-binding assay.[17] Cross-reaction between the species of S antigen was detected by double immunodiffusion using polyclonal rabbit antiserum against bovine S antigen. Reactions of partial identity were obtained for all three proteins. Human and guinea-pig S antigens were labelled with $Na^{125}I$ by the method of Fraker and Speck[18] to a specific activity of 0·16–0·25 MBq/µg.

Enzyme linked immunosorbent assay (ELISA). The assay system was developed using antisera from a known positive antibody secretor with high titres of anti-retinal S antibodies (by Ouchterlony analysis and immunohistochemical analysis). Dynatech microtitre plates were coated with 100 µl purified bovine retinal S antigen (10 g/ml) in 20 mM trometamol (TRIS) HCl, pH 7·5. Preliminary checkerboard analysis indicated that higher concentrations of protein did not increase the sensitivity of the assay. Plates were washed throughout the procedure with 0·2 M trometamol-saline buffer, pH 7·4, containing 0·05% Tween 20. Blocking of free binding sites was achieved with 0·5% bovine serum albumin (in 0·02 M trometamol). Antisera for testing were diluted in 33% newborn calf serum/trometamol Tween pH7·4. Peroxidase labelled rabbit antihuman IgG was diluted 1 in 500 in normal sheep serum and incubated at room temperature for two hours. Enzyme substrate, O-phenylenediamine 0·04%, was diluted in citrate-phospate buffer containing 1 ml H_2O_2 and incubated with the bound antibody for 30 min. The reaction was then stopped with 4 N H_2SO_4, and the absorbence read at 490 nm.

Table 1 *Anti-S antibodies (ELISA)*

Patient category	*n*	*Serum dilution (A_{490})*	
		1:30	*1:100*
Controls	24	0·85 (0·46)*	0·42 (0·29)
Acute iridocyclitis	36	0·65 (0·35)	0·24 (0·17)
Posterior uveitis (all causes)	43	0·92 (0·33)	0·41 (0·20)
Birdshot/focal choroidretinopathy	8	0·86 (0·32)	0·42 (0·23)
Chronic intraocular inflammation	17	0·99 (0·31)	0·41 (0·20)
Retinal vasculitis	7	1·07 (0·24)	0·52 (0·21)
Sarcoid uveitis	6	0·82 (0·31)	0·36 (0·14)

*Mean with SD in parentheses.

Isoelectric focusing. Human sera were analysed by isoelectric focusing (IEF) as described by Williamson.[19]

Reverse immunoblotting. Focused antibodies from IEF gels were transferred to nitrocellulose membranes by an adaptation of the method of Towbin *et al.*[20] as described previously.[13] Blockage of free binding sites on the membrane was achieved with 10% sheep serum in phosphate buffered saline prior to autoantibody detection using homologous labelled S antigen (10^6 cpm/ml). After extensive washing the membranes were dried and bound antigen detected by exposure to Kodak X-omatic S1 *x*-ray film with an Ilford fast tungstate intensifying screen at −70°C, followed by development in Kodak LX 24 developer.

Results

ELISA

A total of 79 patients with uveitis (36 anterior, 43 posterior uveitis) were studied (Table 1) in addition to 24 normal healthy controls. No significant differences were observed in antiretinal S antibody titres between controls and any of the groups. In general, patients with acute iridocyclitis had anti-S antibody titres lower than the controls, while within the subgroups of patients with posterior uveitis the patients with retinal vasculitis had values towards the higher range detected in controls. The most interesting finding, however, was that within the controls, titres of antiretinal S antibody as high as those found in patients with active posterior uveitis were found, indicating that autoantibodies to retinal S antigen occur within the normal population (Fig. 1). No significant differences were detected on dilution of the sera, indicating that these results were not due to non-specific binding of irrelevant immunoglobulin to the microtitre plates.

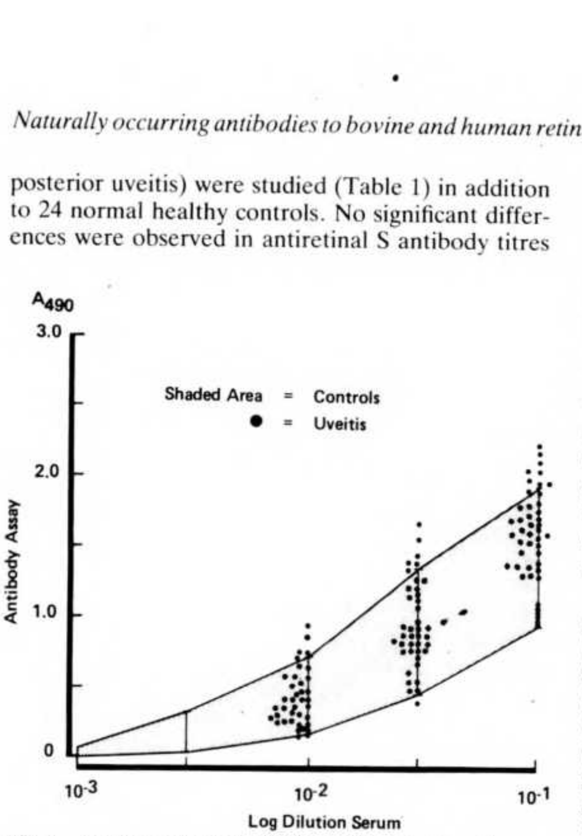

Fig. 1 *Serum anti-S antibodies in uveitis patients and controls as measured by ELISA (see 'Materials and methods'). Ordinate: A_{490} readings from wells of microtitre plate, indicating increasing amounts of bound anti-S antibodies. Abscissa: dilutions of serum. Shaded area= mean±SD of A_{490} values for the group of 24 controls.*

SPECTROTYPE ANALYSIS

Polyclonal antibody responses appear as diffuse non-separable bands of immunoglobulins on isoelectric focusing gels whereas monoclonal immunoglobulin focuses as discrete (3–6) bands of protein.[19] The technique of reverse immunoblotting, where the focused immunoglobulin is transferred to a nitrocellulose membrane and reacted with labelled antigen,[21] has allowed clonal analysis of the antibody response to high molecular weight antigens (>10 K). Fig. 2 shows that sera from patients and controls produced a predominantly polyclonal pattern of antibodies against human retinal S antigen, focusing mainly between pH 7·0 and 8·5. Most sera were

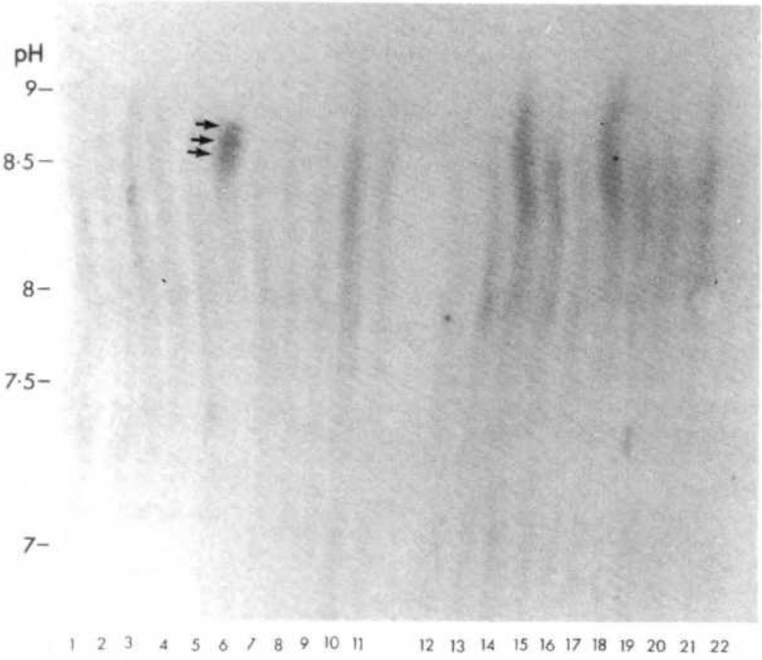

Fig. 2 *Isoelectric focusing gel using reversed immunoblotting procedure (see 'Materials and methods') showing antibody reactions against ^{125}I-labelled human S antigen. Polyclonal staining is indicated by diffuse, variably dark pattern in each of the serum samples (tracks 1–19). Track 6 from a retinal vasculitis patient shows superimposed monoclonal, three banded pattern (arrows). (Tracks 1, 2, 21, 22 controls; tracks 3–20 uveitis patients).*

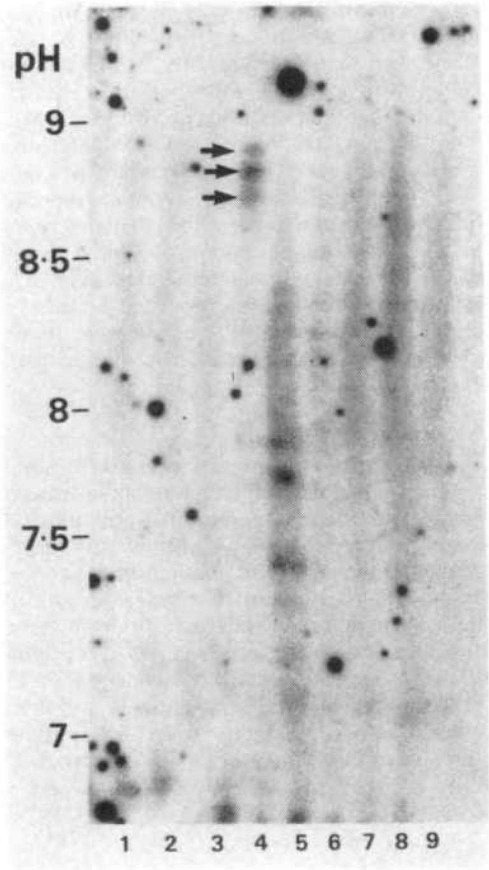

Fig. 3 *Isoelectric focusing gel using the same focused human serum immunoglobulins as in Fig. 2 but against ^{125}I-labelled bovine S antigen. Note similar immunoreactive monoclonal bands in track 4.*

weakly polyclonal, the variation in intensity of antigen binding usually reflecting their corresponding ELISA results. Sera from two patients showed dominant clones (one is shown on track 6, Fig. 2) both in the basic region of the fluorograph against a polyclonal background. When the same sera were overlaid with ^{125}I-labelled bovine retinal S antigen similar patterns, including the two sera with dominant clonotypes, were obtained although with higher background (Fig. 3). This indicates that the clones of lymphocytes responding to human S-antigen recognise the same epitope on bovine S-antigen.

Discussion

The presence of natural autoantibodies is well established in normal adult humans and laboratory mice,[22-25] but their function and relevance to autoimmune disease are not clear. Recent studies suggest that there may be a separate class of B lymphocytes (Lyb 1$^+$ B cells) which are involved solely in secreting autoantibodies.[26] Autoantibodies may be directed towards ubiquitous cellular proteins, for example, anti-DNA antibodies in SLE or to specific targets such as the acetylcholine receptor (AchR) in myasthenia gravis. However, high levels of anti-AchR antibodies may occur in the absence of myasthenia gravis,[27] while active disease may occur in the absence of AchR antibodies.[28] The results of the present study indicate that a similar situation obtains in idiopathic uveitis. Recent studies have indicated that idiopathic endogenous uveitis may have a large autoimmune component[29] with various retinal antigens, particularly S antigen, identified as target antigens for autoreactivity.[30] However, antibodies to retinal S antigen occur equally in patients with endogenous posterior uveitis as well as acute iridocyclitis, as in normal healthy controls (Table 1, Fig. 1). Furthermore, the titre of retinal S antibodies does not correlate either directly or indirectly with disease activity.[4]

In their study of retinal vasculitis Dumonde *et al.*[8] suggested that antiretinal antibodies may have a protective role, since they observed an inverse correlation between disease activity and circulating immune complexes. Cohen and Cooke[31] have taken the concept of natural autoantibodies one stage further and suggest that autoantibodies may serve a protective function generally by acting as a filter to 'blind the immune system' to invading foreign antigens which may fortuitously possess epitopes cross-reactive with self. Evidence for cross-reactivity between bacterial antigens and self-antigens is accumulating,[32 33] and natural autoantibodies which recognise the cross-reacting epitope could block the autoimmune response before it could be augmented by the other immune enhancers (for example, adjuvants, foreign determinants) present on the microbe. Indirect links between uveitis and microbial diseases are well known, and, if Cohen and Cooke are correct, a search for common antigenic determinants may yield valuable data.

An important distinction between natural autoantibodies and autoantibodies associated with disease may be the class of immunoglobulin. Natural autoantibodies tend to be IgM which have a short half-life and could therefore be continuously secreted, while disease-associated autoantibodies tend to be IgG.[34] Study of the class of autoantibody may therefore be helpful in determining its relevance to the disease. Another approach is to study clonal secretion of antibody, for instance, by spectrotypic analysis. Previous studies have shown that clonal restriction of antibody secretion is more likely to occur in non-organ-specific than in organ-specific autoimmune disease.[13] In the present study autoantibody secretion in uveitis was also predominantly polyclonal, though monoclonal responses were observed in two patients with retinal vasculitis, and in both cases the restriction was to an epitope common to both human and bovine S-antigen (Figs. 2, 3). Experimental studies indicate that the antibody response to S-antigen in guinea-pig uveoretinitis is highly restricted, and shared spectrotypes were observed in some animals, suggesting that the antibodies are derived from a limited V-gene pool.[15] A similar restriction may account for the variable susceptibility of humans to uveitis.

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Book Review

Keratoprostheses. By S N Fyodorov, Z I Moroz, V K Zuev. Pp. 143. £29·95. Churchill Livingstone: Edinburgh. 1987.

In 1877 von Hippel reported on the use of keratoprostheses in seven patients. He and others of his time had almost 100% failure owing to extrusion, fistulisation, infection, aseptic corneal necrosis, and retroprosthetic membranes Cynics would say that there has been little progress since.

In this small book Fyodorov reviews the history of keratoprostheses and describes his own modified design He uses a two-stage procedure Firstly, a perforated titanium supporting plate is inserted between corneal lamellae without entering the anterior chamber. Three months later a full thickness central plug of cornea is trephined out and an optical cylinder of polymethyl methacrylate is screwed into the supporting plate.

Fyodorov's indications for surgery are interesting. As well as treating chemical burns and vascularised corneas, where penetrating keratoplasty is relatively contraindicated, he also elects to perform keratoprosthesis in patients with 'endothelial-epithelial dystrophies' such as aphakic and pseudophakic bullous keratopathy. The reason for this is that penetrating keratoplasties in such patients 'are almost always diminished by opacification of the transplant '

His results are better than may be imagined Although the percentage of postoperative complications 'remains high,' only about 10% of prostheses in vascularised corneas extrude (over an average follow-up period of 4·4 years). Visual acuity of better than 6/12 (with limited field) occurs in 30% of his patients at some time postoperatively, though many of these subsequently lose vision secondary to complications.

Unfortunately this book suffers from poor English, muddled layout, and almost anecdotal reporting of clinical results. Fyodorov's showing no awareness of the success of modern penetrating keratoplasty techniques for bullous keratopathy is astonishing. His keratoprosthesis probably represents an improvement on other designs Perhaps the technique should be performed more often on carefully selected cases. Read this book for an insight into Soviet ophthalmology

B L HALLIDAY

Correspondence

Sudden visual loss associated with clostridial bacteraemia

Sir, I was interested to learn that only two cases of endogenous clostridial panopthalmitis had been published prior to the report by Cannistra *et al.*,[1] as a similar case was seen at our hospital. The patient, a 38-year-old lorry driver, presented on 22 January 1987 with sudden onset of pain in the left eye associated with headache, nausea, and vomiting. The previous September his optician had reported that the vision in the left eye had decreased from 6/6 to 6/12, but could find no ocular abnormality, and from that time the patient had also noted diplopia with torsion. The left vision had deteriorated markedly one month prior to his presentation

On examination the patient was afebrile with no evidence of systemic disease The visual acuities were 6/5 right with myopic correction and no perception of light in the left. The right eye was normal. On the left there was marked conjunctival congestion and corneal epithelial and stromal oedema The anterior chamber was almost flat, the lens hazy, and the fundus could not be visualised. Intraocular pressures were 18 mm Hg right and 70+ mm Hg left. Treatment for acute glaucoma with intravenous acetazolamide and intensive pilocarpine was commenced.

The next day the patient was mildly pyrexic The eye remained painful and injected, and the corneal oedema was unchanged. The anterior chamber was deeper but there was a 3-4 mm hyphaema. Peripheral anterior synechiae were noted inferiorly, and the intraocular pressure was 40 mm Hg. Signs of orbital cellulitis developed over the next 24 hours, with proptosis, severe periorbital oedema, and gross restriction of ocular movement. Blood cultures were taken, and treatment with intravenous gentamicin and ampicillin was commenced, along with topical chloramphenicol and oral prednisolone. Full blood examination revealed a neutrophil leucocytosis of $18{\cdot}8\times10^9$/l. The findings on CT scan were consistent with an orbital cellulitis, and no space occupying lesion was identified Sinus *x*-rays were normal.

By the following day (three days after presentation) the pain had decreased and the lid oedema had lessened, but there was still marked conjunctival chemosis, corneal oedema, and hyphaema. *Clostridium perfringens* was grown from the blood culture, and intravenous therapy was changed to penicillin and cephalexin. The orbital cellulitis settled rapidly, but the hyphaema was replaced by an obvious hypopyon. Within two months the eye became phithisical A hyphaema recurred 12 months after presentation, and the patient continues to suffer from recurrent episodes of chemosis and pain in the left eye.

The case was similar in many ways to the one presented by Cannistra *et al.*, but the history of visual loss and diplopia over several months was suggestive of a low grade infection that suddenly took a fulminant course.

R HARRISON

The General Hospital,
New Street,
Burton-on-Trent,
Staffordshire DE14 3QH

Reference

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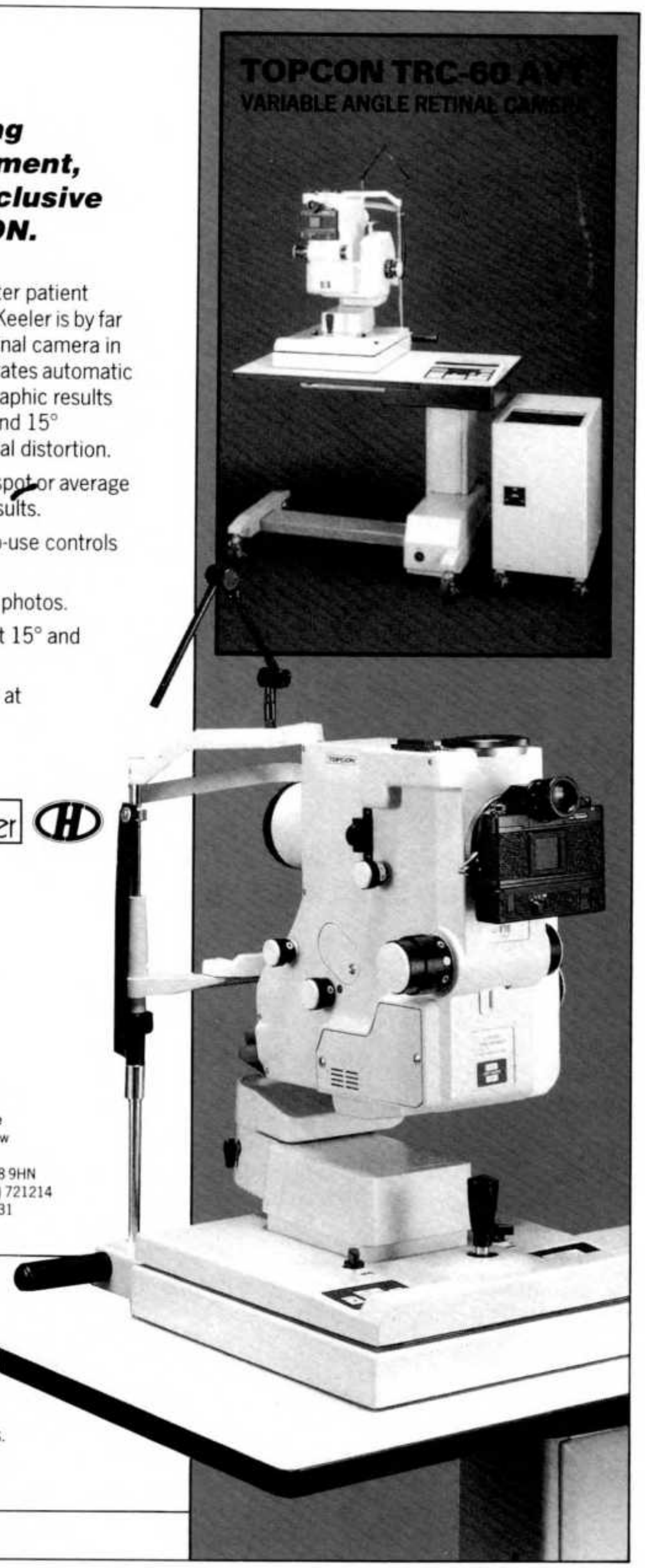

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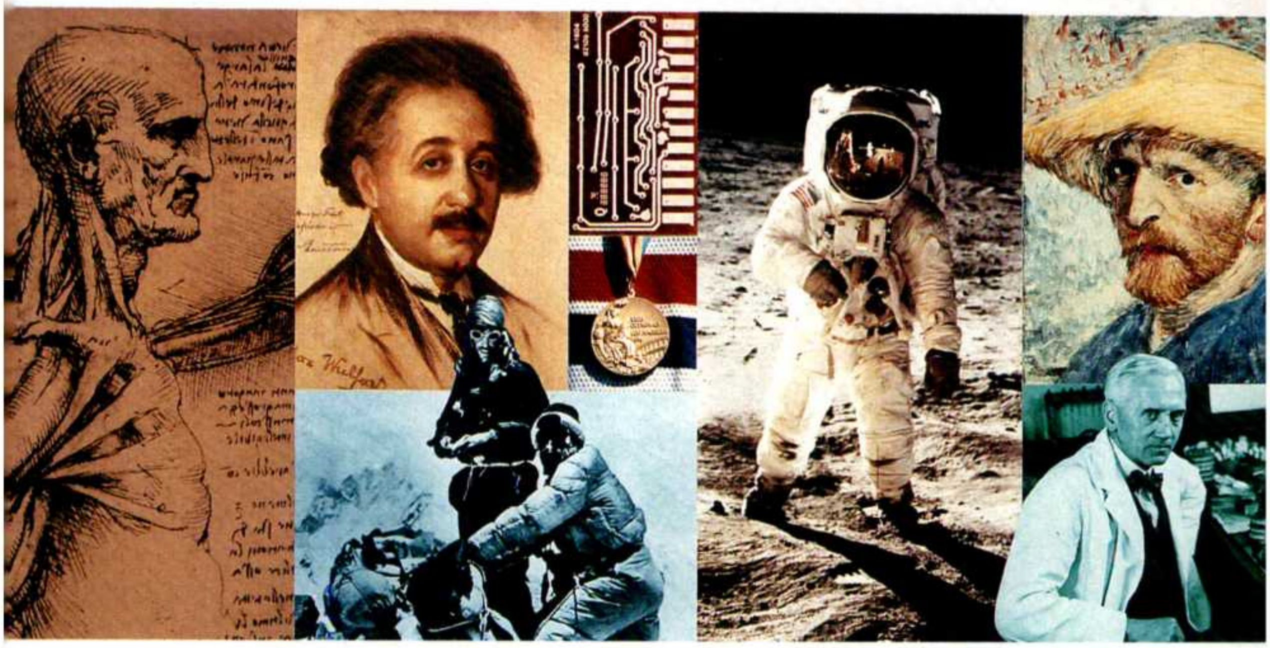

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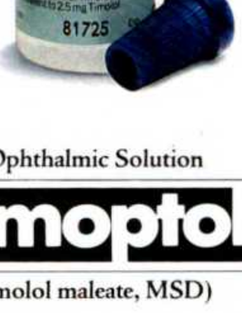

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PRESCRIBING INFORMATION: DOSAGE AND ADMINISTRATION: The usual dose is one drop instilled twice daily. If necessary concomitant therapy with pilocarpine, other miotics, adrenaline or systemically administered carbonic anhydrase inhibitors can be instituted. **CONTRA-INDICATIONS:** Betoptic is contra-indicated in patients with sinus bradycardia greater than a first degree block, cardiogenic shock or a history of overt cardiac failure and in patients with hypersensitivity to any component. **WARNINGS:** Patients who are receiving a beta-adrenergic blocking agent orally and Betoptic should be observed for potential additive effect either on intra-ocular pressure or the known systemic effects of beta-blockade. While Betoptic, a cardioselective beta-blocker has demonstrated a low potential for systemic effects, it should be used with caution in patients with a history of obstructive pulmonary disease, in patients with diabetes (especially labile diabetes) or in patients suspected of developing thyrotoxicosis. Consideration should be given to the gradual withdrawal of beta-adrenergic blocking agents prior to general anaesthesia because of the reduced ability of the heart to respond to beta-adrenergically mediated sympathetic reflex stimuli. This product contains benzalkonium chloride and is not recommended for use when soft contact lenses are being worn. **DRUG-INTERACTIONS:** Although Betoptic used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with Betoptic and adrenaline has been reported occasionally. Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or bradycardia. Caution should be exercised in patients using concomitant adrenergic psychotropic drugs. **ADVERSE REACTIONS:** Although Betoptic is generally well tolerated, discomfort of short duration may be experienced by some patients upon instillation and occasional tearing has been reported. Rare instances of decreased corneal sensitivity, erythema, itching, corneal punctate staining, keratitis, anisocoria and photophobia have been reported. Systemic reactions following topical administration of Betoptic (eg: insomnia and depressive neurosis) have only rarely been reported. **USE IN PREGNANCY:** Although some animal studies have not demonstrated any specific hazard there are no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response this drug should be used during pregnancy only if clearly indicated. **USE BY NURSING MOTHERS:** It is not known whether Betoptic is excreted in human milk, caution should therefore be exercised when Betoptic is administered to nursing mothers. **TREATMENT OF OVERDOSAGE:** A topical overdose of Betoptic may be flushed from the eye(s) with warm tap water. **PRODUCT LICENCE NUMBER: 0649/0097**

British Journal of Ophthalmology, 1989, **73**, 161

Editorial: Cellular debris—a key to the aging macula

The greatest socioeconomic problem confronting the Western World is the progressive aging of its population. This change presents special problems for the ophthalmologist, as all surveys show a dramatic increase of prevalence of blindness with increasing age. A review of the principal diagnoses given in relation to blind registration in people over 65 shows that almost 50% of blind registrations result from macular disease.

It is perhaps significant that over the last few years many research groups throughout the world have directed their efforts towards understanding the aging processes occurring in the outer retina. Many studies seem to indicate that with increasing age the constant renewal of the light sensitive membranes of photoreceptor cells may present problems for the retinal pigment epithelium and in turn Bruch's membrane.[1] The implications are that the constant phagocytosis of disc membranes and their subsequent degradation by lytic enzyme systems within the pigment epithelium eventually result in the progressive accumulation of debris within pigment epithelial cells.[2] By the fourth decade extracellular debris is also seen accumulating in the innermost layers of Bruch's membrane. Sarks[3] has elegantly demonstrated in her clinicopathological studies that in many individuals the extracellular deposits, possibly genetically predetermined, play a significant part in the generation of age related macular disease. The spectrum of disturbances in the aging retina ranges from extensive subpigment epithelial deposits, through drusen, to pigment epithelial detachments and subretinal neovascular complexes. Extracellular debris may not only be a causal agent in loss of function in the aging macula, but may also account for some of the variations or patterns seen on clinical examination.

A recent paper[4] has postulated as a causal agent the constant deposition of the waste products of phospholipid degradation by the pigment epithelium, eventually resulting in an aggregation of lipid within the innermost layers of Bruch's membrane, the presence of such a hydrophobic layer impeding the passage of water moving from the retina towards the choroid.[5] In elderly people such a barrier may well be the causal agent of pigment epithelial detachments, in that as the pigment epithelium pumps water from the subretinal space towards the choroid it literally pumps itself off Bruch's membrane.

Clinically, Hoskin *et al*[6] subdivided pigment epithelial detachments into those in which hyperfluorescence of the detached pigment epithelium was uneven and those in which it was even. This subdivision was considered an important indicator in prognosis, as even hyperfluorescence indicated a predisposition for the detached epithelium to rip. The authors postulated that the dichotomy in clinical appearance of these two types of detachments may arise through differences in cleavage planes as the cells leave Bruch's membrane. Detachments with uneven hyperfluorescence were postulated to occur as a result of the pigment epithelium becoming detached from Bruch's membrane and taking with it both its basement membrane and some of the underlying extracellular debris which generally lies between the basement membrane and the inner collagenous layer of Bruch's membrane. In contrast in those lesions with even hyperfluorescence the concept was that the pigment epithelium became detached, leaving its basement membrane behind.

The scanning electron microscope study presented in this issue by Yamamoto and Yamashita is of particular interest in relation to the possible locations of differential cleavage planes within Bruch's membrane. Although the cleavage planes illustrated result from deliberate histological techniques, they show clearly that the pigment epithelium can be displaced from its basement membrane and that the basement membrane itself may be detached from the underlying inner collagenous layer of Bruch's membrane, and, in its becoming so, debris lying between the basement membrane and the inner collagenous layer may either remain on the collagenous layer or become detached from it and adhere to the basement membrane of the pigment epithelium.

JOHN MARSHALL

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Scanning electron microscopic observation of Bruch's membrane with the osmium tetroxide treatment

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SUMMARY Scanning electron microscopic observation of Bruch's membrane was performed after removal of retinal pigment epithelium (RPE) with the osmium tetroxide treatment. Eight human eyes from subjects at various ages (from newborn to 77 years old) were examined in order to investigate aging changes in Bruch's membrane. The collagen fibres of the inner collagenous zone in young eyes formed a tightly interwoven membrane, and the meshes were regular and fine. In old eyes the meshes were irregular and coarse, and deposits were observed. Deposits were embedded in the collagen fibres of the inner collagenous zone, or attached to the surface on the inner-collagenous-zone side of the basement membrane of RPE.

Bruch's membrane and its aging changes have been observed mainly by light and transmission electron microscopy (TEM)[1-9] Scanning electron microscopic studies have been few, probably because it is technically difficult to remove retinal pigment epithelium (RPE) from Bruch's membrane without damage. Goldbaum and Madden digested RPE with trypsin and observed Bruch's membrane by scanning electron microscopy (SEM).[10] In the present study RPE was removed with the osmium tetroxide treatment,[11] and Bruch's membrane was observed by SEM. In addition, Bruch's membranes at various ages were examined in order to investigate aging changes.

Material and methods

One eye was obtained from each of eight patients. Table 1 lists the age and cause of donors' death or surgical enucleation. Six eyes were obtained at necropsy (cases 1–6). The eyes were enucleated and fixed in 2·5% glutaraldehyde 6 to 12 hours post mortem. The other two eyes (cases 7 and 8) were enucleated under general anaesthesia because of retinoblastoma and immediately fixed in 2·5% glutaraldehyde. The osmium tetroxide treatment was carried out according to the method of Komuro and Uehara.[11] After fixation in 2·5% glutaraldehyde the eyes were dissected into fragments of appropriate size, and specimens containing macular regions were immersed in 2% osmium tetroxide solution, which was buffered to pH 7·4 with 0·1 M cacodylate buffer, for 4 to 7 days at 4°C. After this treatment the cells became fragile, so RPE cells were washed off Bruch's membrane with a jet stream of osmium tetroxide solution from a pipette.

For SEM the specimens were dehydrated with a graded series of ethanol, critical-point-dried, coated with platinum-vanadium, and observed by SEM (ISI-DS 130, Akashi, Japan). For TEM a part of each specimen was dehydrated with a graded series of ethanol and embedded in Epok 812 (Oken Shoji, Japan). Ultrathin sections were cut, stained with uranyl acetate and lead nitrate, and observed by TEM (JEM 1200EX).

Table 1 *Eight eyes of eight individuals used in this study*

Case	*Age (years)*	*Comments*
Necropsied cases		
1	Newborn	Infantile sudden death
2	11	Brain tumour
3	23	Sudden death after delivery
4	56	Cerebral haemorrhage
5	66	Gastric cancer
6	77	Cerebral infarction
Eyes surgically obtained		
7	0	Retinoblastoma
8	2	Retinoblastoma

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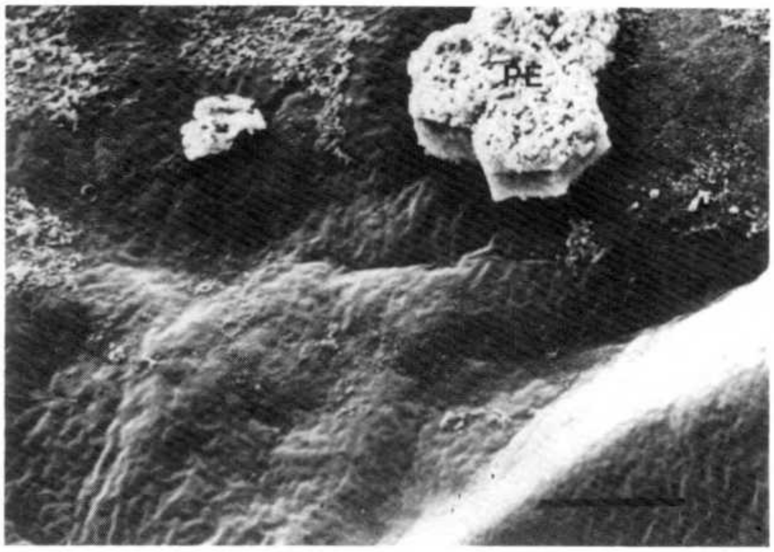

Fig. 1 *Basement membrane of RPE in a 23-year-old patient (case 3). PE: Patches of pigment epithelium remaining attached to Bruch's membrane. Bar=10 μm.*

Results

After the osmium tetroxide treatment the tissue, especially the cell components, became fragile and could be easily removed. As shown in Fig. 1, RPE cells were removed and the basement membrane of RPE cells was exposed. In some specimens the basement membrane of RPE was torn and the inner collagenous zone was exposed. The ground substance in the inner collagenous zone was washed off and the collagen fibre could be observed by SEM (Fig. 2).

In the Bruch's membrane of the young eyes (from the newborn to the 11-year-old patients) the collagen fibres in the inner collagenous zone formed a tightly interwoven membrane. The meshes were regular and fine. Deposits were absent in the inner collagenous zone on SEM observation (Figs. 2, 3). In Bruch's membrane of the old eyes (from the 56- to the 77-year-old patients) the collagen fibres in the inner collagenous zone also formed an interwoven membrane, but the meshes were irregular and coarse, and the collagen fibres were inclined to aggregate and to form bundles in contrast to the young eyes (Figs. 4, 5, 6).

Among the collagen fibres in the inner collagenous zone of the old eyes, deposits of various kinds were

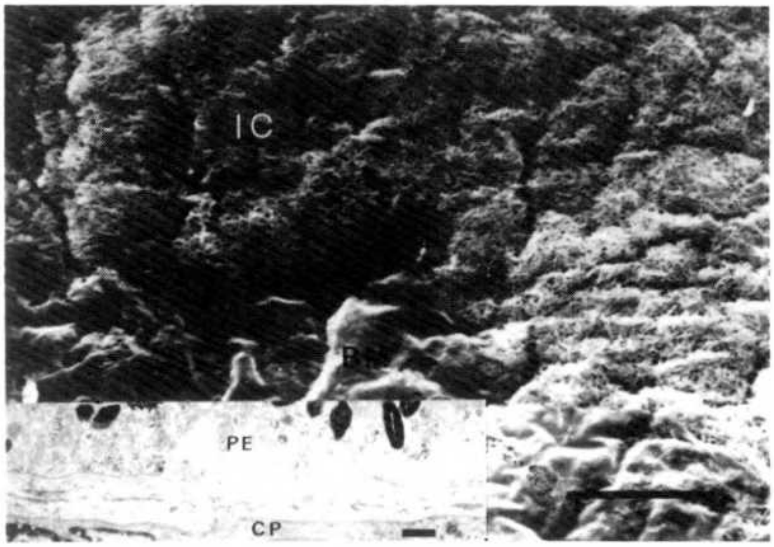

Fig. 2 *Where basement membrane of RPE* (BM) *is absent, the inner collagenous zone* (IC) *is exposed. The meshes of tight interweaving of collagen fibres are regular and fine. Deposits are absent. A newborn infant (case 1). Bar=10 μm.* Inset: *Transmission electron micrograph of Bruch's membrane in same patient (case 1). Deposits are absent.* PE: *Retinal pigment epithelium.* CP: *choriocapillaris. Bar=1 μm.*

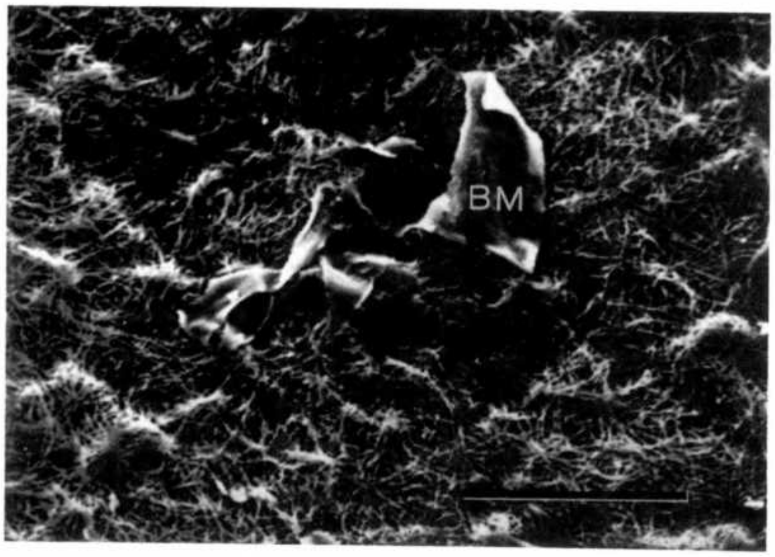

Fig. 3 *Inner collagenous zone in a 2-year-old patient (case 8). The meshes of tighly interweaving collagen fibres are regular and fine. Deposits are absent.* BM: *Basement membrane of RPE. Bar=10 μm.*

observed (Figs. 7, 8). As shown in Fig. 7, spherical structures and larger structures of other shapes were embedded in the collagen fibres. A mound-like structure, shown in Fig. 8, had a rather smooth surface and involved the surrounding collagen fibres. This was observed to project from the inner collagenous zone toward the RPE. Similar deposits were also observed to be attached to the surface on the inner-collagenous-zone side of the basement membrane of RPE (Figs. 5, 6).

The results of the observations by SEM coincided with those by TEM, that is, deposits were absent in Bruch's membrane of the young eyes (Fig. 2, inset), and deposits were noted in the old eyes (Fig. 9). In Fig. 9 vesicular and tube-like structures, wide-spacing collagen, and so on were observed.

Discussion

With the osmium tetroxide treatment the tissues, especially the cell components, become fragile and can be easily removed.[11] This technique is thought to be useful for removing the overlying cells and observing the underlying tissue.[12] In this report Bruch's membrane was observed by SEM after removal of RPE. In some specimens the inner collagenous zone

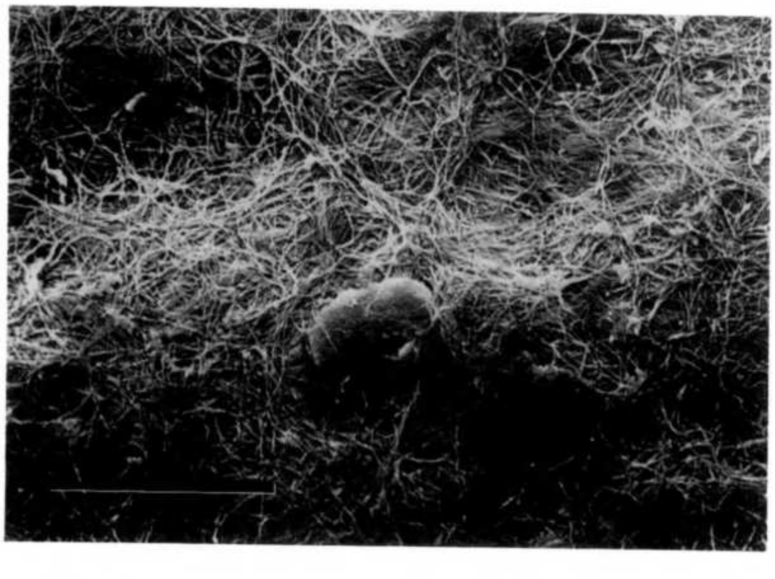

Fig. 4 *Inner collagenous zone in a 56-year-old patient (case 4). The meshes are irregular and coarse. The collagen fibres aggregate and form bundles. Bar=10 μm.*

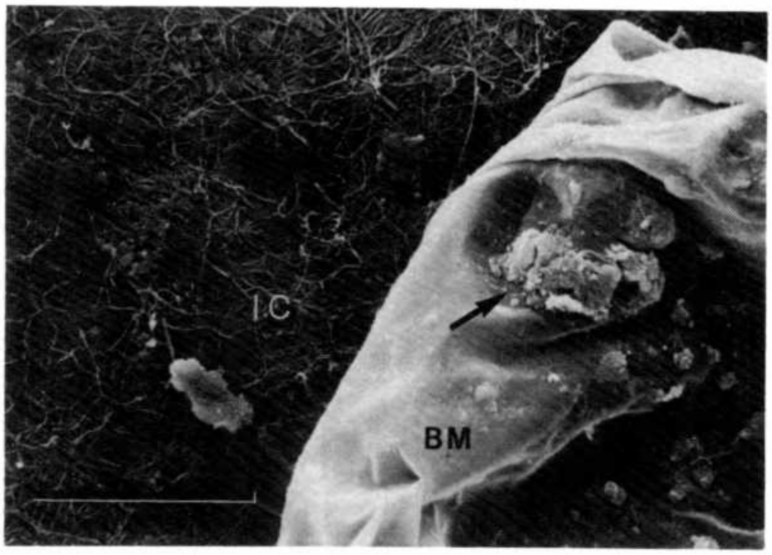

Fig. 5 *The inner-collagenous-zone-side surface of basement membrane of RPE* (BM) *and inner collagenous zone* (IC) *in case 4. Deposits are noted in the collagen fibres of* IC *and attach to* BM *(arrow). Bar=10 μm.*

was exposed because the basement membrane of the RPE was torn. Examination of Bruch's membrane by SEM after osmium tetroxide treatment showed that the meshes of a tightly interwoven membrane formed by the collagen fibres of the inner collagenous zone were regular and fine in the young eyes but were irregular and coarse in the old eyes. In the old eyes the collagen fibres in the inner collagenous zone tended to aggregate and to form bundles in contrast to those in the young eyes. The increase of collagen fibre cross-links was detected biochemically with increasing age in various organs.[13 14] The changes of the inner collagenous zone observed by SEM might be related to the aging of collagen of this type.

Deposits in the inner collagenous zone in the old eyes observed by SEM are thought to correspond to those observed by TEM. A mound-like structure (as shown in Fig. 8) was observed to project towards the RPE, and this is thought to correspond to a druse. While the deposits shown in Figs. 7 and 8 were embedded in the inner collagenous zone, the deposits shown in Figs. 5 and 6 were attached to the basement membrane of the RPE. Adhesion between the latter deposits and the basement membrane may be strong. The interpretation of this is obscure. Observations by TEM revealed that some deposits were located

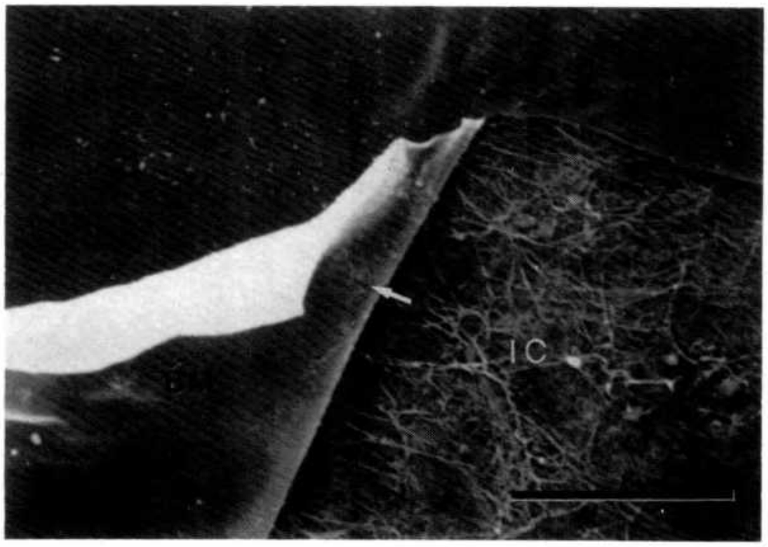

Fig. 6 *Basement membrane of RPE* (BM) *and inner collagenous zone* (IC) *in a 77-year-old patient (case 6). Deposits attached to the inner-collagenous-zone-side surface of basement membrane of RPE (arrow). Bar=10 μm.*

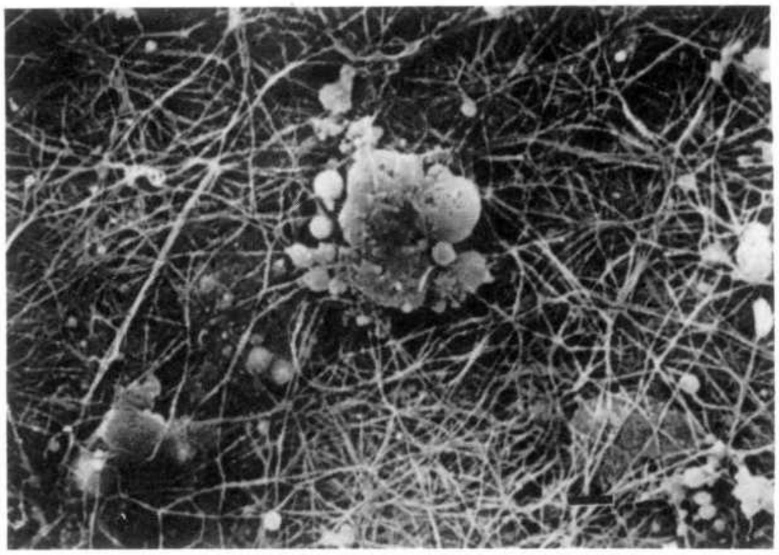

Fig. 7 *Inner collagenous zone in a 56-year-old patient (case 4). Deposits are noted among the collagen fibres. Bar=1 μm.*

beneath the basement membrane of RPE. Some authors suggested that bulk release (apoptosis) of pigment epithelial cytoplasm leads to the formation of some deposits.[5,7,9] The deposits shown in Figs. 5 and 6, or at least some of them, may correspond to those.

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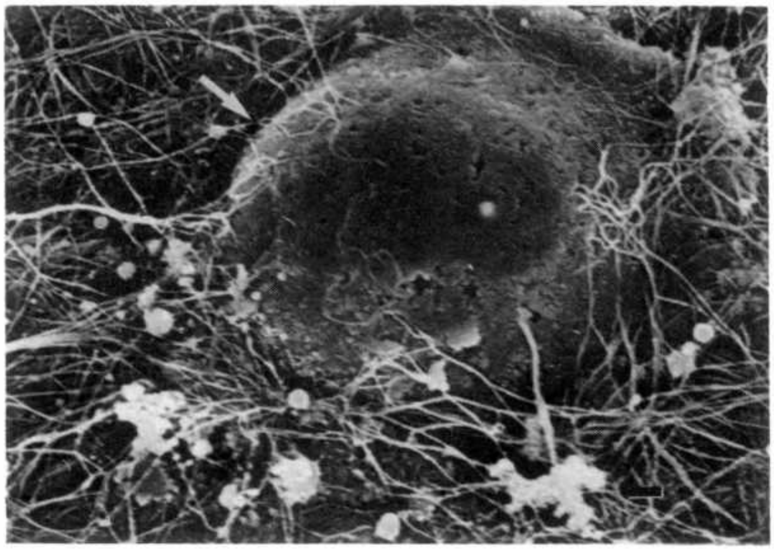

Fig. 8 *Inner collagenous zone in case 4. A mound-like structure is noted (arrow). Bar=1 μm.*

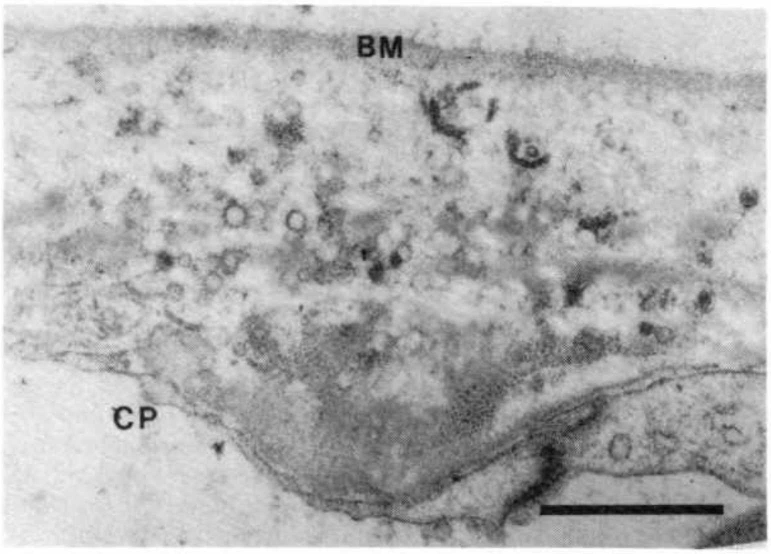

Fig. 9 *Transmission electron micrograph of Bruch's membrane in case 4. Deposits are noted.* BM: *Basement membrane of RPE.* CP: *Choriocapillaris. Bar=1 μm.*

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Rhodopsin-induced experimental autoimmune uveoretinitis in monkeys

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SUMMARY We present the first evidence that purified rhodopsin can induce experimental autoimmune uveoretinitis (EAU) in monkeys. Injection of a highly purified lipid-free rhodopsin preparation provokes severe chorioretinitis with concomitant anterior uveitis. The onset of disease is earlier, its frequency is higher, and the inflammation is considerably more severe than in EAU induced under similar conditions by opsin. The first inflammatory cells are observed in the ciliary body and pars plana. Within a few days the inflammation extends into the anterior chamber, choroid, and retina. Retinitis predominates in the central area, while chorioretinitis is observed in the periphery, both accompanied by damage to and elimination of the photoreceptor cells. The monkeys develop high cellular and humoral immune responses against rhodopsin and opsin. The cellular response maximum just precedes the onset of EAU. This may indicate that cellular immunity has an important role in the pathogenesis of rhodopsin-induced EAU.

Autoimmune reactions against retina-specific proteins are suspected of playing an important part in the pathogenesis of uveitis. Uveitis-like disease can be experimentally induced in animals such as the rat and guinea-pig by injection of these proteins.[1-10] As such the model of experimental autoimmune uveoretinitis (EAU) is useful in studies of the pathogenesis of uveoretinal disorders as well as of the role of autoimmune reactions in these processes. As a model for human disease, primates are of particular interest in this kind of studies. In purified form, S-antigen,[11 12] opsin,[13] and IRBP (interphotoreceptor retinoid-binding protein)[14 15] have been reported to induce uveoretinitis in monkeys.

Recently we have presented evidence that in Lewis rats rhodopsin is considerably more pathogenic than opsin.[8] Here we present the first report on the induction of uveoretinitis in monkeys by pure rhodopsin. The clinical state, histological changes, and cellular and humoral immune responses of the injected animals have been evaluated.

Materials and methods

PREPARATION OF ANTIGENS

For the induction of EAU highly purified lipid-free rhodopsin was prepared as described previously.[8 16] A reconstituted rhodopsin preparation was used as test antigen.[8] All procedures involving rhodopsin were performed under dim red light (λ>620 nm). In order to prepare opsin, a rhodopsin preparation was illuminated just before use by means of a 100 W tungsten lamp at 30 cm distance for 10 minutes at room temperature. Bovine S-antigen and IRBP were prepared as described previously.[10 17]

IMMUNISATION, CLINICAL OBSERVATION, AND HISTOLOGICAL EVALUATION

Four young adult female stump-tailed macaques (*Macaca artoides*) were each injected with 650 μg rhodopsin under dim red light. About 400 μg of antigen was emulsified in Freund's complete adjuvant (Difco, Detroit) and injected subcutaneously at 10 sites interscapularly. The rest of the antigen was injected intraperitoneally in 1 ml pertussis vaccine (*Haemophilus pertussis*; 5×10^9 micro-organisms, 1·25 mg aluminium hydroxide, Pasteur Institute, Paris). The animals were housed under darkroom conditions for the first 10 days after injection and subsequently housed under normal diurnal light-dark conditions (12h light:12h dark). Under these conditions the subcutaneously injected rhodopsin was protected against light effects during the critical phase of exposure to the immune system. Experi-

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ments with rats showed that housing in darkness for a period of eight days is sufficient to achieve this goal. Housing in darkness itself has no detectable influence on the development of rhodopsin-induced EAU.[8 11] From day 10 after injection the clinical signs of uveitis were monitored by slit-lamp examination. Occasionally the fundi were examined by indirect ophthalmoscopy.

For histological examination animals were killed at various stages of the disease (Table 1). The eyes were fixed in Bouin fluid, embedded in paraffin, and 5 µm sections were stained with haematoxylin and eosin.

IMMUNE RESPONSES

The humoral and cellular immune responses were determined weekly using enzyme-linked immunosorbent assay (ELISA) and lymphocyte transformation test (LTT), respectively. In the latter assay, rhodopsin, opsin, and S-antigen were applied as test antigens. In the ELISA, IRBP was used as an additional test antigen. Optimal antigen concentrations were determined in previous experiments.

The ELISA was carried out essentially as described before[3] with a reconstituted rod outer segment membrane preparation containing 5 pmol rhodopsin (based on absorbance spectroscopy) per ml buffered saline (0·02 M phosphate, pH 7·6) to coat the wells.

Cellular immune responses were determined by means of lymphocytes separated from heparinised blood by lymphocyte separation medium (Boehringer, Mannheim). The lymphocyte transformation test was carried out as described previously[4] with 10% heat-inactivated monkey serum in the culture medium and 5 µg test antigen per ml cell suspension. All samples were manipulated under dark room conditions until the cells were harvested.

Table 1 *Clinical features of rhodopsin-induced uveoretinitis in monkeys*

Monkey no	*Day of onset*	*Day of listed scores*	*Slit-lamp score**			
			Left eye†		*Right eye†*	
			AC	*VIT*	*AC*	*VIT*
L64	21	21	0	0	2+	2+
L70	23	24	2+/3+	3+	1+	2+
L76	24	31	4+	NV	2+	2+
L77	24	24	0	1+	0	0
		41	2+	2+	3+	4+
		48	3+	2+	3+	2+
		55	1+	1+	2+	1+
		70	0	1+	0	1+

*Score on the day the animal was killed (L64, L70, L76) and in addition for L77 also at other days when the eyes showed typical characteristics of inflammation as listed Scores: 1+, a few cells in aqueous and/or vitreous, 2+, cells in the aqueous and moderately dense cell infiltration of the vitreous, 3+, cells and protein in the aqueous, dense cell infiltration of the vitreous, poor fundal view, 4+, dense cell infiltrations in the vitreous blocking the fundal view, protein precipitates and many cells in the aqueous. †AC=anterior chamber. VIT=vitreous. NV=not visible.

Results were expressed as stimulation indices (SI):

SI=counts per minute in presence of antigen/counts per minute in absence of antigen.

A stimulation index >2 was considered to be positive.[4]

Results

CLINICAL EVALUATION

Each of the four monkeys injected with rhodopsin developed clinical signs of uveitis within 21–24 days of injection (Table 1). The first clinical features were slight cell infiltrations in anterior chamber and

Table 2 *Review of histopathological features of rhodopsin-induced EAU in monkeys*

Days post-injection	*Eye**	*Severity of inflammation†*						
		AC‡	*CB/PP‡*	*Periphery*		*Central*		
				Choroid	*Retina*	*Choroid*	*Retina*	*ON‡*
21	L64 OS	1+	1+	0	0	0	0	0
24	L70 OD	1+	1+	0	0	0	0	0
21	L64 OD	1+/2+	2+	3+/4+	3+/4+	0	0	0
24	L70 OS	2+	2+	3+/4+	3+/4+	0	0	0
31	L76 OD	1+	1+	4+	4+	0	0	0
31	L76 OS	3+	3+	4+	4+	3+/4+	3+/4+	1+
70	L77 OS	1+	1+	4+	1+	2+	3+/4+	2+
70	L77 OD	2+	1+	4+	1+	1+/2+	3+/4+	2+

*Monkey number and scored eye are indicated OS=left eye OD=right eye

†Histological scores· 0, normal tissue, 1+, a few inflammatory cells; 2+, mild cell infiltration without tissue damage, 3+ to 4+, dense cell infiltrations with mild to severe tissue damage

‡AC=anterior chamber CB=ciliary body. PP=pars plana ON=optic nerve

vitreous. Mild uveitis (score 1+/2+) developed into a severe (score 3+/4+) panuveitis within two weeks of onset (L76 and L77). The anterior chamber was seriously affected at that stage, and dense cell infiltrations combined with the Tyndall phenomenon impaired observation of the vitreous and fundus. The iris was only slightly affected, while adherence to the lens was not observed. At this stage the retinopathy consisted of an arterial and venous perivasculitis accompanied by sheathing of the retinal blood vessels and a focally oedematous retina. In addition, oedema and hyperaemia of the optic disc were observed. About six weeks after clinical onset the inflammatory cells had disappeared from the anterior segment of monkey L77, but some inflammatory cells remained in the vitreous.

HISTOPATHOLOGY

At least unilateral severe disease was found in all the animals except L64, which was killed in the early stage. In all monkeys the first signs of ocular inflammation appeared between days 21 and 24 after injection. In all cases the disease followed a similar course in the mild, early stages. The results of the histopathological examination are summarised in Table 2.

Initial stage. At the first signs of clinical onset a few mononuclear cells were present in the anterior chamber, ciliary body, and pars plana, while in the rest of the eye no signs of inflammation were detected (L64 OS and L70 OD; Table 2).

About one day after onset (slit-lamp score 1+/3+, L64 OD and L70 OS) we observed mainly focal peripheral chorioretinitis. Dense infiltrations consisting of mononuclear and many polymorphonuclear cells were locally present in choroid and retina together with perivasculitis. The anterior chamber, ciliary body, and pars plana showed a mild infiltration with mononuclear and polymorphonuclear cells, while no inflammatory cells were detectable in the iris.

Severe stage. Dense mononuclear and polymorphonuclear infiltrations were found in ciliary body, pars plana, and ora serrata. Occasionally an accumulation of mononuclear cells was observed in the region of pars plana and ciliary body. The anterior chamber and iris were seriously affected.

Severe oedema was found in the peripheral choroid, while the central part showed moderate oedema (Fig. 1a). Over the whole retina exudates and retinal detachments were observed together with local damage of the photoreceptor cells. At these sites the pigment epithelium was disrupted. The central area of the retina showed the most severe signs of inflammation consisting of mononuclear and many polymorphonuclear cells, perivasculitis, and oedematous areas in the inner and outer nuclear layers (Fig. 1b). The optic nerve head showed mild perivasculitis of the major central retinal vessels.

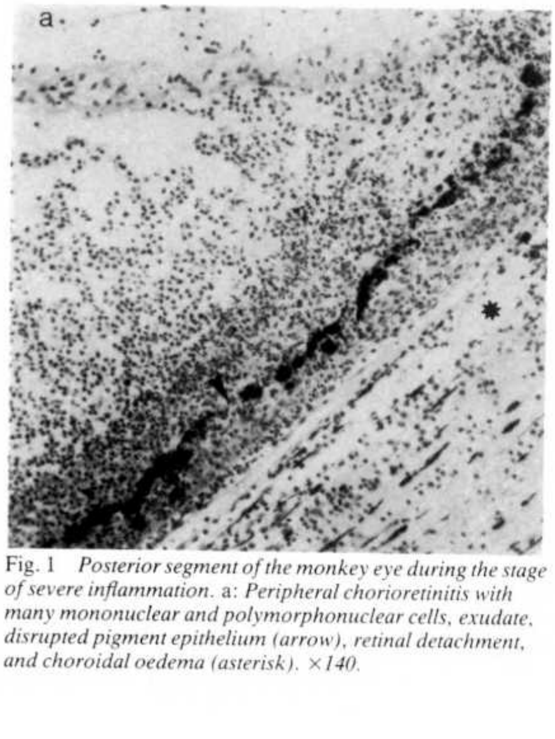

Fig. 1 *Posterior segment of the monkey eye during the stage of severe inflammation.* a: *Peripheral chorioretinitis with many mononuclear and polymorphonuclear cells, exudate, disrupted pigment epithelium (arrow), retinal detachment, and choroidal oedema (asterisk).* ×*140.*

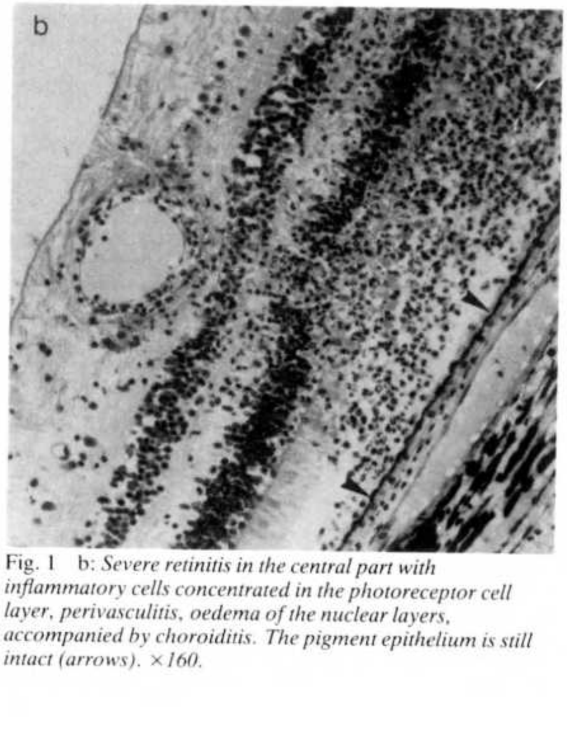

Fig. 1 b: *Severe retinitis in the central part with inflammatory cells concentrated in the photoreceptor cell layer, perivasculitis, oedema of the nuclear layers, accompanied by choroiditis. The pigment epithelium is still intact (arrows).* ×*160.*

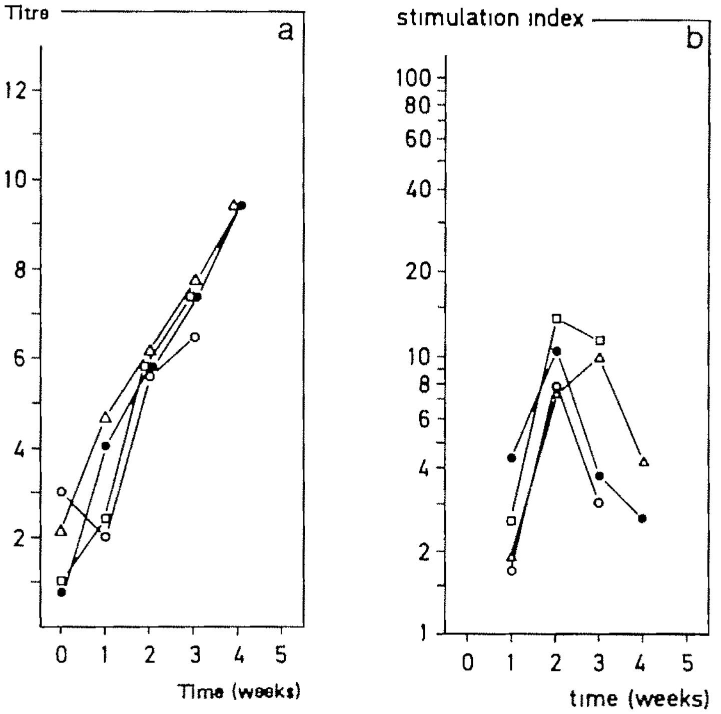

Fig. 2 *Immune responses of monkeys injected with rhodopsin.* a: *Antibody titres were determined by ELISA*[8] *Titres were determined graphically as the dilution of serum required to give an absorbance over a background of 0·5. A dilution of 1.50 corresponded to a titre of 1, 1.100 to a titre of 2, 1·200 to a titre of 3, and so on Preimmune sera had a titre of 1* b. *Stimulation indices were determined by LTT, with rhodopsin as test antigen (in darkness) Symbols designate monkey L64 (○), L70 (□), L76 (△), and L77 (●)*

Regression stage. Seven weeks after onset of uveitis, when the disease was in the regression stage (L77, Table 1), signs of severe inflammation were still present in retina and choroid. The pigment epithelium showed extensive focal damage, with dispersion of pigment. The photoreceptor cells were severely damaged or eliminated. In general, retinitis dominated in the posterior pole of the eye, while severe chorioretinitis was observed at the periphery.

IMMUNE RESPONSES

As test antigens rhodopsin and opsin produced equal results in the immunological assays, and only the values obtained with rhodopsin are presented (Fig. 2). The time course of the development of the antibody titres showed a similar pattern for all animals (Fig. 2a). The titres continued increasing up to at least 3–4 weeks after injection. The antibody titre of monkey L77 reached a maximum level of about 11 in week 6. This level was maintained for the subsequent weeks until the animal was killed (not plotted). No antibodies against S-antigen or IRBP were detectable by ELISA.

The cellular immune responses as determined by the lymphocyte transformation tests showed a different pattern (Fig. 2b). The stimulation indices also increased sharply during the first two weeks after injection but then appeared to level off (L70 and L76) or to decrease (L64 and L77). The stimulation indices determined in week 4 for the remaining two monkeys confirmed this trend. The stimulation index of monkey L77, which was measured until week 10 after injection, fluctuated during weeks 5–10 after injection round an average value of 5 (SD 3; n=5).

Discussion

PATHOGENICITY OF RHODOPSIN

Highly purified rhodopsin appears to be markedly pathogenic in *Macaca artoides*. In our laboratory an equal dose of opsin was recently shown to induce severe EAU in only two out of nine macaques with much later onset (6–10 weeks).[11] We therefore conclude that in monkeys rhodopsin is considerably more pathogenic than opsin, which agrees with results obtained recently in rats.[8 18 19]

CLINICOPATHOLOGICAL FEATURES OF RHODOPSIN-INDUCED EAU

In comparison with opsin-induced uveoretinitis in the monkey,[11] rhodopsin evokes a more severe chorioretinitis and an increased involvement of the anterior chamber, similar to that observed for S-antigen [11 12] The histological changes share some characteristics with those described for S-antigen-induced EAU in cynomolgus monkeys, such as vasculitis and chorioretinitis, which is active for a long period.[11] This contrasts with the lack of choroidal involvement in S-antigen-induced EAU in monkeys reported by Nussenblatt *et al.*[12]

IMMUNE RESPONSES

Monkeys injected with rhodopsin showed a high cellular and humoral immune response against both rhodopsin and opsin. The humoral response appeared not to have reached its maximum level at the time of onset of disease (days 21–24 after injection). In monkey L77 the antibody titre steadily increased until five to six weeks after injection. The stimulation index, however, appeared to level off or peak just before clinical onset of disease. This may indicate that the cellular immune response has an important role in the pathogenesis of rhodopsin-induced EAU in primates, as was also found in various forms of EAU in the rat.[8,10] This is in accordance with the generally accepted idea of EAU being a model of a T-cell-mediated autoimmune disease.

We are grateful to Mrs E D Kuhlmann for her expert technical and secretarial assistance and to Dr A J J M Rademakers for funduscopy

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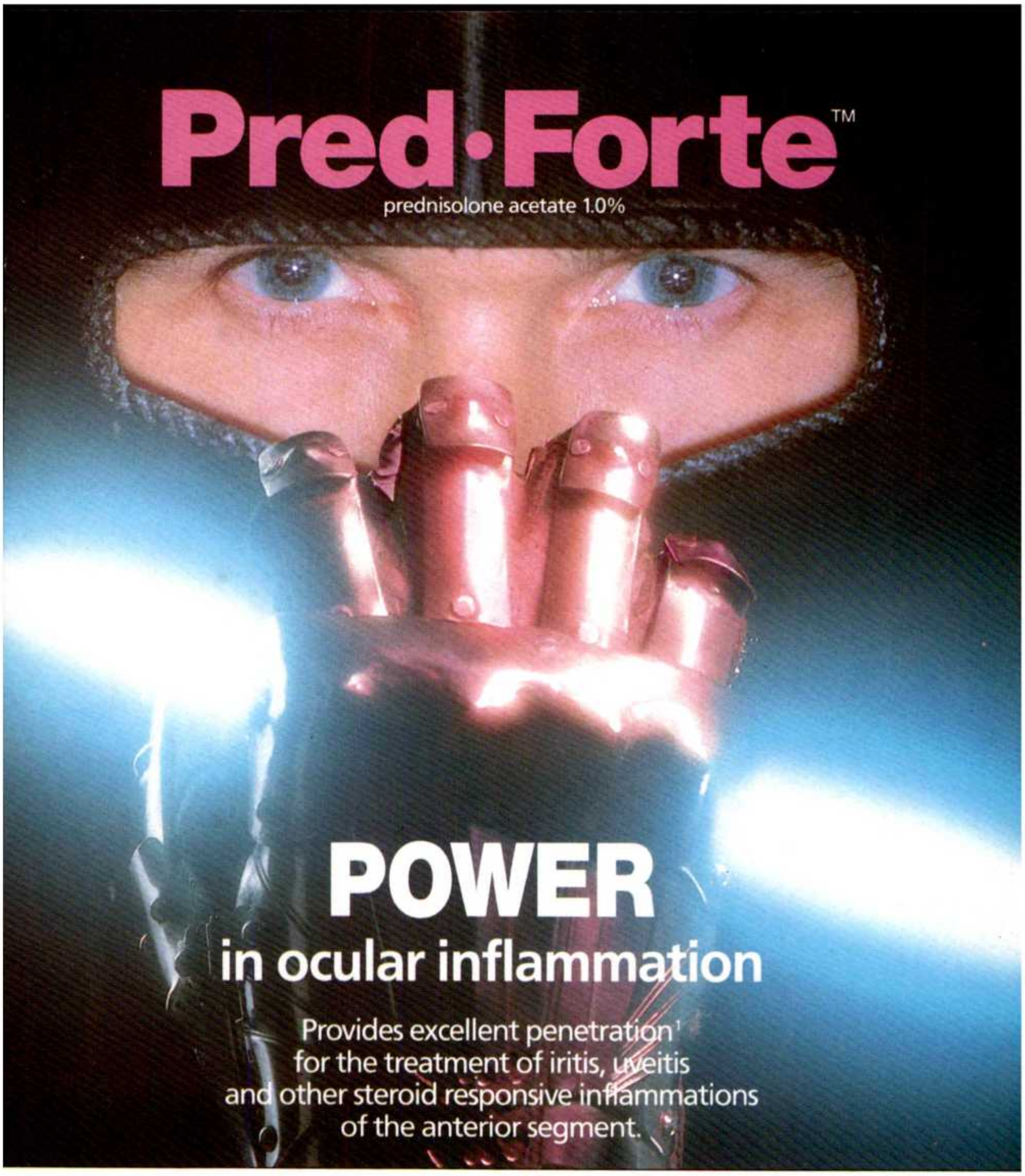
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Product Licence number: 0426/0051.

Date of preparation: February 1988.

Reference 1. Leibowitz HM, Berrospi AR, Kupferman A. Am J of Ophthalmology 1977; **83**(3): 402-406.

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The use of Glauline is not recommended in patients with obstructive airway disease, cardiac failure or hypersensitivity to metipranolol. Beta blockers should not be given with verapamil and neither drug should be administered within several days of discontinuing the other. As absorption into the circulation is possible, Glauline should only be used with caution in patients already receiving similar drugs by mouth. In particular, care should be taken in patients with sinus bradycardia an greater than first degree heart block. Although there is no evidence t suggest that metipranolol has teratogenic properties, its use during pregnancy should be avoided, unless the potential benefits are considered to outweigh the possible hazards. No clinical trials in children have been carried out. Glauline should not be used in patients fitted with soft (hydrophilic) contact lenses.

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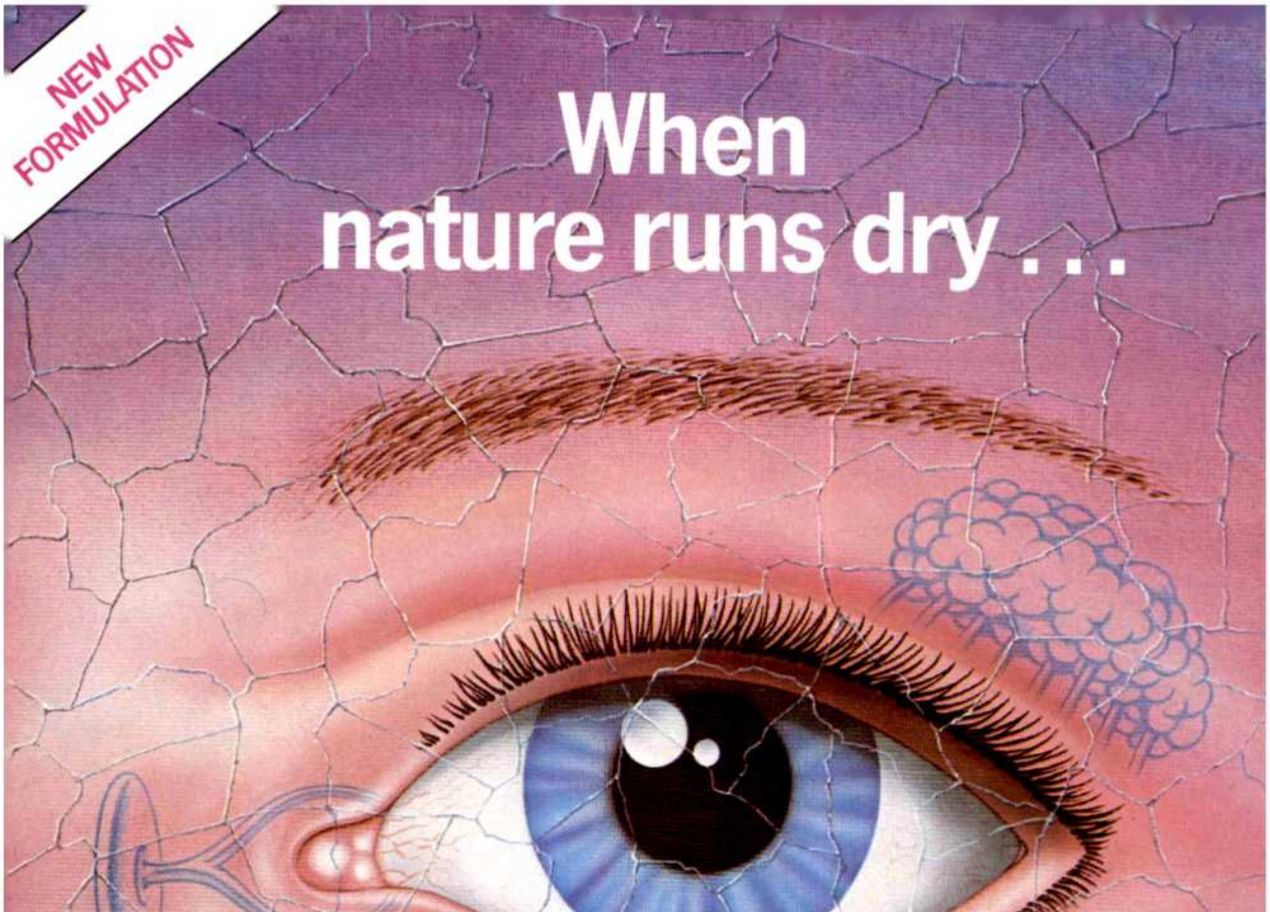
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British Journal of Ophthalmology, 1989, **73**, 173–176

Allopurinol use and the risk of cataract formation

WALTER K CLAIR, LEO T CHYLACK JR, E FRANCIS COOK, AND LEE GOLDMAN

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SUMMARY Several reports have suggested an association between chronic allopurinol ingestion and cortical and subcapsular cataract formation. To examine this possibility we identified 51 allopurinol users and compared their lenses with those of 76 patients who did not use allopurinol. The existence of lens opacities and the level of visual acuity were assessed by review of medical records or by prospective ophthalmic examinations; in both phases of the study the examiners were blinded as to the patient's use or non-use of allopurinol. Three different outcomes were considered: formation of any cataract, formation of a posterior subcapsular cataract, and formation of a cataract contributing to a corrected visual acuity of 20/30 or worse. The risk ratio for the formation of any cataract was 1·3 (95% confidence interval: 0·8, 2·0), the risk ratio for the formation of a posterior subcapsular cataract was 0·9 (0·3, 2·0), and the risk ratio for the formation of a cataract contributing to a loss of visual acuity was 1·3 (0·6, 2·9). None of these risk ratios was changed appreciably after controlling for age, sex, hypertension, or diabetes. Thus, after a mean of 6·9 years of allopurinol use, we found no evidence to confirm that allopurinol users were at higher risk of acquiring cataracts.

Cases reported to the National Registry of Drug-Induced Ocular Side Effects[1] have suggested an association between allopurinol use and cortical and subcapsular cataract formation. Lerman *et al.*[2] demonstrated that allopurinol is photobound in the human lens and suggested that it is cataractogenic in patients in whom this photobinding has occurred. Although Jick and Brandt[3] found no association between allopurinol use and cataract surgery, their study did not include ophthalmic examinations. To find out whether allopurinol use increases the risk of cataract formation we designed a study that included ophthalmic examinations.

Patients and methods

RETROSPECTIVE PHASE

From hospital pharmacy records we identified 457 allopurinol users without concomitant chemotherapy, including 56 who had received an ophthalmic examination at our institution. After excluding patients whose examinations preceded allopurinol use, or whose records suggested a history of congenital cataracts, ocular disease, ocular trauma, or exposure to toxic cataractogenic agents (n=26), or whose examinations did not include a lens examination (n=6), we had 24 allopurinol users for this phase of the study. By the same exclusion criteria we identified 54 allopurinol non-users from among all patients who had been referred for ophthalmic examination prior to the initiation of amiodarone or hydroxychloroquine therapy.

PROSPECTIVE PHASE

Of the 401 allopurinol users without ophthalmic examinations in the retrospective review 193 who were known to be alive and in the proximity of our hospital were invited to receive a free examination: 159 declined, six did not keep a scheduled appointment, and one was excluded by the same criteria used in the retrospective phase, leaving 27 allopurinol users in the prospective phase. Ophthalmic examinations to assess visual acuity and lens opacities were also performed on 22 non-users of allopurinol who were recruited from our hospital based internal medicine practice.

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BASELINE INFORMATION

By medical record review (retrospective phase) or patient interview (prospective phase) we obtained each patient's sex; age at the ophthalmic examination; history of diabetes, hypertension, or glaucoma; use of birth control pills, oestrogens, miotic medications, or phenothiazines; and occupation. No records or interviews suggested congenital cataracts, ocular disease, ocular trauma, or exposure to cataractogenic agents.

OPHTHALMIC EXAMINATION INFORMATION

From the medical records in the retrospective phase and the detailed ophthalmic examinations in the prospective phase we recorded each patient's initial, corrected, and best corrected Snellen visual acuity; nuclear colour as pale yellow, yellow, dark yellow, or brown/black; existence or previous removal of cataracts; evidence of injury or inflammation; and presence of retinopathy (diabetic retinopathy or maculopathy).

Cataracts were divided into four major classes—nuclear, cortical, supranuclear, and posterior subcapsular. Age related changes such as cortical flecks and isolated vacuoles, lamellar separations, and sutural prominence were not classified as cataracts, nor were Mittendorf dots. If the cortical, supranuclear, or subcapsular opacity was visible at the slit-lamp against the red reflex, and if it consisted at least of linear or clustered aggregates of the flecks, vacuoles, and lamellar separations, it was designated a cataract. Patients with a best corrected Snellen visual acuity of 20/30 or worse as a result of retinal disease were excluded. Retrospective information was obtained from medical records without any knowledge of allopurinol use. Similarly, information obtained from all prospective ophthalmic examinations was determined without knowledge of allopurinol use.

Three aspects of cataract existence were considered as possible outcomes: the development of any cataract, posterior subcapsular cataracts, or cataracts that contributed to a best corrected visual acuity of 20/30 or worse. Because of inadequate medical record information, five allopurinol users and four non-users in the retrospective phase could not be classified as to their best corrected visual acuity and were eliminated in the analyses for this outcome.

STATISTICAL METHODS

All numbers and analyses were based on patients, not individual eyes. Estimated risks for cataract development were compared by the χ^2 test.[4] Risk ratios and corresponding 95% confidence intervals were constructed.[5] In the one instance where an estimated risk for non-users equalled 0·0, 0·5 was added to the numerator of this risk.[5] Potential confounding by age, sex, diabetes, and hypertension was controlled by two methods: a logistic regression model that expressed each outcome as a function of allopurinol use and the potential confounders[5]; and a propensity score analysis,[6] by which patients were stratified by their likelihood for allopurinol use, according to subranges of a logistic regression model that expressed allopurinol use as a function of the confounders. Power calculations for detecting relevant values for the risk ratio were based on the non-null distribution of the test statistic in the usual χ^2 test of association.[4] Increased risk for cataract formation with increased duration of allopurinol use was examined by a χ^2 test for trend.[7]

Table 1 *Distribution of age, sex, diabetes, and hypertension for allopurinol users and non-users*

	Allopurinol users (n=51)	*Non-users (n=76)*
Age		
Mean (years)	61 8	57·6
Standard deviation	12 4	12 2
Male sex	38 (75%)	27 (34%)
Diabetes	13 (25%)	5 (7%)
Hypertension	27 (53%)	26 (34%)

Results

Allopurinol users were older and contained more males, more diabetics, and more hypertensives than non-users (Table 1). Estimated risk ratios were similar for the two phases of the study, except for the formation of a posterior subcapsular cataract (Table 2), where these estimated risk ratios had the widest confidence intervals. Therefore, because of the strong similarities of results in the two data sets, all further analyses were based on the single combined data set.

Compared with non-users the allopurinol users did not appear to have an excess risk for any of the three outcomes. Adequate data on the exact duration of allopurinol use were available for 37 of the 51 allopurinol users. The mean duration of use was 6·9 years, standard deviation 6·9 years. Only seven patients had used allopurinol for more than 10 years. No tendency for increased risk of cataract formation with increased duration of allopurinol use was observed for any of the three outcomes. When potential confounding by age, sex, diabetes, and hypertension was controlled both by logistic regression and by propensity score analyses, the adjusted risk ratios remained non-significant and were very similar to the crude estimates. Our sample size is

Table 2 *Estimated risks and risk ratios for the formation of any cataract, of a posterior subcapsular cataract, or of a cataract contributing to loss of visual acuity* for allopurinol users compared with non-users in retrospective, prospective, and combined data sets*

Data set	*Number of subjects*	*Any cataract*		*Posterior subcapsular cataract*		*Cataract leading to loss of visual acuity*	
		Risk	*Risk ratio*	*Risk*	*Risk ratio*	*Risk*	*Risk ratio*
Retrospective							
Users	24	0·33	1·1 (0·5, 2·1)†	0·17	0·9 (0·3, 2·6)†	0·32	1·6 (0·7, 3·8)†
Non-users	54	0·31		0·19		0·20	
Prospective							
Users	27	0·52	1·3 (0·7, 2·4)	0·04	2·5 (0·3, 21·6)	0·11	2·4 (0·3, 20·4)
Non-users	22	0·41		0·00		0·05	
Combined							
Users	51	0·43	1·3 (0·8, 2·0)	0·10	0·9 (0·3, 2·0)	0·20	1·3 (0·6, 2·9)
Non-users	76	0·34		0·13		0·15	

*Cataract contributing to corrected visual acuity 20/30 or worse †95% Confidence interval.

sufficient for detecting large effects of allopurinol on all three outcomes (for example, RR=3·0) and small effects (for example, RR=1·5) for any cataract (Table 3) but insufficient for detecting small effects for posterior subcapsular cataracts or cataracts contributing to a best corrected visual acuity of 20/30 or worse.

Discussion

March *et al.*[8] demonstrated that oxipurinol, an allopurinol metabolite, enters the human lens. Using high-resolution phosphorescence spectroscopy, Lerman *et al.*[12] showed that allopurinol is photobound in the human lens. They have suggested that this leads to photosensitisation and subsequent cataract formation. Our study differs from the report by Jick and Brandt,[7] who found no association between allopurinol use and surgery for cataract extraction, because our patients had full ophthalmic examinations by methods shown to be valid, reproducible, and sufficiently sensitive.

We did not find evidence of a major increase in risk for any of three types of cataracts among users of allopurinol. One potential problem is possible misclassification of the presence or absence of a cataract in our retrospective phase. However, all determinations of outcome obtained from medical records were obtained without knowledge of allopurinol use, and therefore any misclassification would be expected to be random, that is, independent of allopurinol use. The strong similarities in results from both study phases, despite different methods for detecting outcomes, makes it unlikely that there was any substantial random misclassification bias, especially since the prospective phase strictly followed a valid and reproducible classification system.[10-14]

Another possible explanation for the negative results is a selection bias by which either our allopurinol users or non-users do not reflect the true risks for cataract formation. For example, our non-users with rheumatic conditions may have used aspirin, which may be protective against cataract formation.[15] However, this potential bias would tend to overstate the association between allopurinol use and cataract formation rather than bias it towards the null value. Although our low recruitment rate could potentially introduce bias, we considered it was imperative to include a detailed ophthalmic examination to eliminate an ascertainment bias that might have existed in a study that relied on cataract surgery,[7] rather than on the presence of a cataract. Although it is possible that our negative results are due to an insufficient period of allopurinol use, there was no increased risk for cataract formation with increased duration of allopurinol use.

Finally, our study has a limited ability to identify a true but relatively weak association. Nevertheless, the consistency of the results with those of the prior study[7] argue against a strong association between allopurinol and cataracts.

Table 3 *Power of test of significance for our data set to detect risk ratios of 1·5, 2·0, and 3·0 for the formation of any cataract, of a posterior subcapsular cataract, or of a cataract contributing to loss of visual acuity**

Risk ratio to be detected	*Any cataract*	*Posterior subcapsular cataract*	*Cataract contributing to loss of visual acuity*
1·5	0·52	0·17	0·19
2·0	0·97	0·46	0·50
3·0	0·99	0·92	0·94

*Cataract contributing to corrected visual acuity of 20/30 or worse.

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Pulsed neodymium-YAG laser trabeculotomy: energy requirements and replicability

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SUMMARY Short pulsed laser trabeculotomy has been shown to reduce intraocular pressure in patients with primary open angle glaucoma. This study seeks to determine the energy levels required to produce a fistula into the canal of Schlemm for four different Q-switched neodymium-YAG lasers. The laser was fired at fixed human trabecular meshwork specimens at a range of energy settings for each laser and the characteristics and replicability of the lesions produced were analysed. Energy levels between 3 and 5 mJ were sufficient to produce fistulae into the canal of Schlemm with an approximately 50% success rate for each instrument.

The pulsed neodymium-YAG laser may be used in a variety of ways for the treatment of glaucoma. These have been recently reviewed[1 2] and include peripheral iridotomy, reopening of trabeculotomy, graded trabeculectomy, lysis of synaechiae, cyclodialysis, sclerostomy, goniotomy, and internal trabeculotomy. Short pulsed lased internal trabeculotomy was first described by Krasnov[3] as a means of treating glaucoma. Unfortunately the pressure lowering effects of his treatment were not sustained beyond a few months.

Short pulsed laser trabeculotomy has been performed on a variety of ape species.[4-8] Depending on the type of instrument used, energy levels between 0·5[5] and 305 mJ[4] have been employed to produce a fistula into the canal of Schlemm. However, these studies have shown that there is little resultant effect on intraocular pressure or facility of outflow, and when the lesions heal they are covered by a sheet of endothelial cells with a Descemet-like basement membrane. It has, however, been argued that the failure to reduce normal intraocular pressure in a healthy monkey cannot be compared with the need to restore normal pressure in a patient with glaucoma.[8] Moreover, a fistula through which there is a persistent flow of aqueous owing to a pressure differential would be more likely to remain patent.

Theoretical considerations suggest that 20 perforations of 10 μm diameter between the anterior chamber and the canal of Schlemm should restore normal outflow facility in open angle glaucoma.[9] For clinical studies the type of instrument used, the energy levels chosen, and the number of laser applications required to treat patients with glaucoma by pulsed laser trabeculotomy have hitherto been chosen empirically.[3 10-12] When three to six superimposed laser applications were used, closure of the fistula ensued.[12] However, multiple single laser applications have produced a sustained reduction in intraocular pressure.[10 11]

Owing to microscopic variations in the morphological characteristics of the trabecular meshwork, lesions produced at the same laser energy settings are not entirely replicable, and it has been argued that extensive experimental trial and error methods with electron microscopic evaluation are required to produce data to guide future research.[13] Most of the morphological studies of pulsed laser trabeculotomy have been carried out on lesions produced with specially built apparatus, and the energy levels used are not comparable with those required for instruments which are currently available.

We have recently described the aiming criteria quired to produce a fistula into the canal of Schlemm[14] and have shown that lesions produced in the trabecular meshwork are to a certain extent energy dependent.[15] Moreover, we have demonstrated that the energy levels required to produce a fistula in vivo are similar to those which were determined by in-vitro experiments.[14]

In order to establish guidelines for future clinical

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research we have extended our previous work and have carried out an in-vitro scanning electron microscopic study of short pulsed Nd-YAG laser trabeculotomy lesions, produced by four currently marketed instruments. The energy levels required to produce a fistula into the canal of Schlemm were ascertained, and the replicability of the lesions produced by one or two such energy levels for each instrument were determined.

Materials and methods

Four Q-switched pulsed Nd-YAG lasers were employed. They comprised the Biophysic Médical Nanolas laser using the 10° convergence angle, the Zeiss Visulas laser, the Lasag Microruptor II, and the Lasag Topaz instruments.

Human trabecular tissue was prepared from donor eyes which had not suffered antecedent ocular disease. Tissues were fixed in 3% cacodylate buffered glutaraldehyde, and 2–3 mm wide radial segments of corneoscleral tissue containing the trabecular meshwork were prepared. The ciliary body and iris tissues were removed by sharp dissection from each specimen without disturbing the trabecular meshwork.

A small plastic waterbath was prepared, and a Trokel gonioscopic lens (Ocular Instruments Inc), designed for use with pulsed Nd-YAG lasers, was mounted with a watertight seal into one end. The bath was filled with normal saline. Each specimen was in turn mounted on cardboard and immersed in the bath in such a manner that the trabecular meshwork could be clearly seen with the laser slit-lamp microscope through the centre of the Trokel lens.

Each laser was adjusted to the energy settings described, and the laser was aimed and fired twice at the posterior trabecular meshwork, close to the cut edge at each side of the wedge shaped specimen. This technique permitted subsequent scanning electron microscopic assessment of the lesions in both the transverse and vertical dimensions.

Each specimen was reimmersed in 0·2 M cacodylate buffer and prepared for scanning electron microscopy (Jeol JSMT 2000) by critical point drying and gold coating. Each lesion was then photographed

It was not possible to produce exact measurements of the size of each lesion owing to variations in shape and the difficulty in defining the boundaries of each lesion. Thus lesions were graded both for size and neatness according to the protocol below, in preference to using quantitative but imprecise measurements. Fig 1 illustrates the morphological characteristics of each of these grades

GRADINGS OF ND-YAG LASER LESIONS

Size grade

0 No lesion
1 Superficial trabecular compression or disruption
2 Hole in trabecular meshwork which does not enter the canal of Schlemm
3 Small hole in trabecular meshwork which enters the canal of Schlemm
4 Large hole in trabecular meshwork which enters the canal of Schlemm with or without superficial damage to the outer wall of the canal
5 Hole which perforates the outer wall of the canal of Schlemm

Neatness grade

A Smooth margins to hole
B Ragged margins to hole.

Lesions were independently graded by three observers. The score sheets were collated, the inter-observer repeatability assessed, and overall grades were assigned for size and neatness. These were accorded as follows:

Size grade

(*a*) If unanimous—that grade
(*b*) If 2 out of 3 agreed—the majority grade
(*c*) If all 3 differed—the central grade

Neatness grade

(*a*) If unanimous—that grade
(*b*) If not unanimous, the majority decision

Two experiments were carried out for each of the four lasers. First, between three and six shots were fired at the posterior trabecular meshwork of separate specimens for each setting in a range of energy settings, and the lesions produced were graded. Energy levels required to produce reliably a fistula into the canal of Schlemm without disrupting the outer wall were determined. For the second experiment multiple shots were fired at such an energy level and the lesions produced were assessed in the same manner.

Results

Fig. 1 illustrates the appearances of the gradings described above.

The size gradings assigned by the three assessors for all micrographs were compared. For the 202 micrographs studied 86% of gradings showed at least two out of three in agreement, while for 14% the assessments differed. The χ^2-test was employed to verify that the level of concordance for the gradings was uniform for individual experiments. There was no significant difference ($0{\cdot}2<p<0{\cdot}5$). The neatness gradings demonstrated 40% complete concordance and 60% showed two out of three in agreement. The χ^2-test again confirmed that there was no significant variation between experiments ($p<0{\cdot}5$). These figures indicate that both the gradings and the subjective assessments of neatness employed give satisfactory consistency.

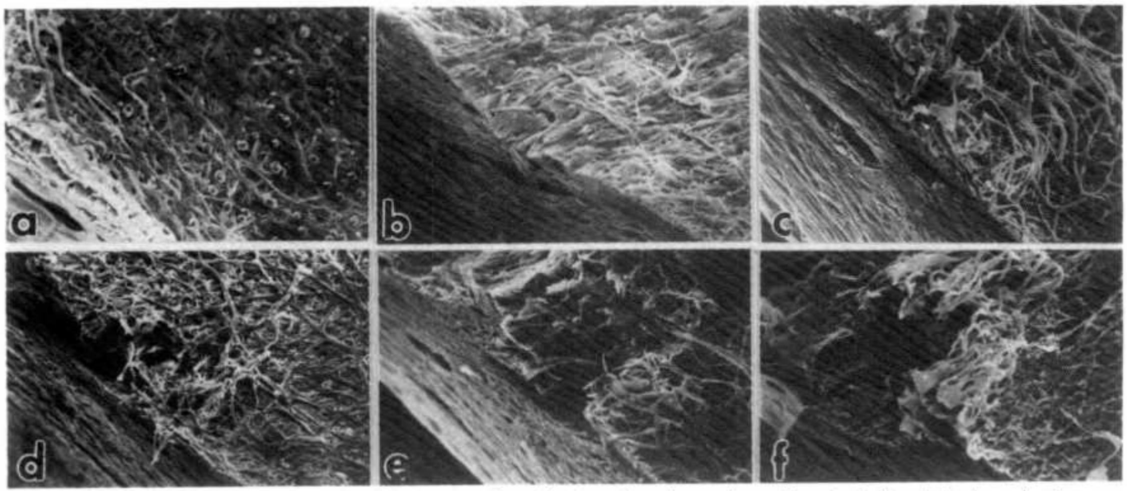

Fig. 1 *Scanning electron micrographs of lesions produced in the trabecular meshwork by single Q-switched neodymium-YAG laser pulses graded according to the protocol described.* a: *Grade 0.* b: *Grade 1.* c: *Grade 2.* d: *Grade 3.* e: *Grade 4.* f: *Grade 5.* ×*170.*

Figs. 2–5 provide a graphical analysis of the grades of the lesions produced in the trabecular meshwork in relation to the energy levels applied with each instrument. The graphs on the left relate to the extent of damage produced by each energy level employed while the graphs on the right provide illustrations of the replicability of the lesions produced for single energy settings. It can be seen that there is no strong correlation between the energy applied and the severity of damage produced. For the Biophysic Médical Nanolas, the Zeiss Visulas, and the Lasag Topaz apparatus grade 4 lesions were produced only with pulses of 3 mJ or more, whereas with the Microruptor II lower energies sufficed to produce such a degree of damage. Apart from this caveat the relationship of the energy levels employed to the lesions produced did not differ in any consistent manner between instruments.

There was no difference between the instruments with respect to the 'neatness' of the lesions produced. Approximately half the lesions were graded as neat and half as ragged for each instrument.

With regard to the replicability of the lesions produced, the likelihood of producing a fistula into the canal of Schlemm with the energy levels selected approximated to 50%, with a slightly higher success rate for the Zeiss Visulas instrument.

Discussion

Before applying short pulsed laser lesions on the trabecular meshwork with the intention of treating glaucoma it is important to establish the energy requirements to produce a patent fistula into the canal of Schlemm without disruption of the outer wall of the canal. Although these requirements have been established for specially built apparatus[16 17] there have been few studies aimed at delineating the energy requirements for commercially available apparatus.[15] Criticisms of the above study include the fact that the tissue was fixed and not fresh, and that the optical system of a waterbath differs from that of the human eye. However, we have recently conducted a study with our own specially built apparatus on patients whose eyes were subsequently enucleated for melanoma and have found that the energy settings which were determined in vitro with fixed tissue[16 17] did not differ significantly from those required to produce a fistula into the canal of Schlemm in vivo.[14] Moreover, the alternative primate experiments are difficult and expensive, and the different morphology of the trabecular meshwork makes the results difficult to interpret and extrapolate for use in man. The disparity in the grading assessments apportioned by the three authors in the present study arose as a result of the difficulties in definitively interpreting the degree of tissue disruption. Nevertheless, the results obtained indicated that, although the extent of tissue damage is partly energy dependent, there is considerable variation between shots at the same energy levels.

The instruments which were investigated differ considerably both in design and construction and in price. The features most likely to be potential causes of differing performance of the lasers are pulse duration (7 ns for Visulas, 5 ns for Nanolas, and 12 ns for Topaz and Microruptor II), beam convergence angle (12° for Visulas, 10° selected for the Nanolas,[15]

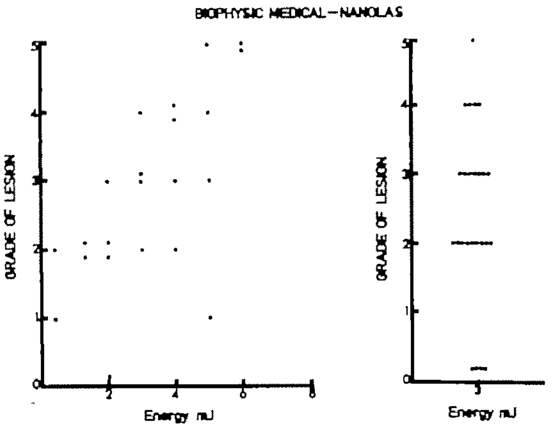

Fig. 2 *Graphs relating the grades of the lesion produced in the trabecular meshwork in relation to the laser energy applied with the Biophysic Médical Nanolas laser. The graph on the left illustrates the results obtained for a range of energy settings and the graph on the right illustrates the replicability of the lesions produced at a single energy setting*

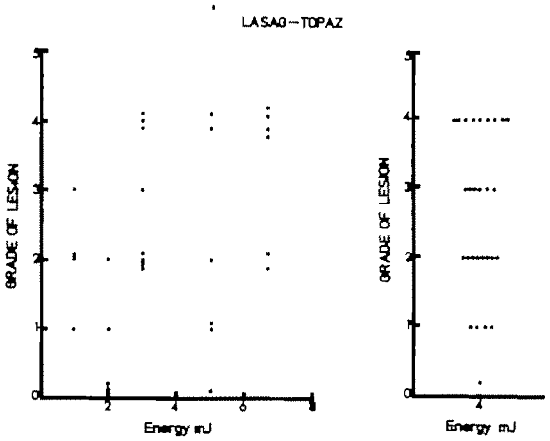

Fig 4 *Graphs relating the grades of the lesion produced in the trabecular meshwork in relation to the laser energy applied with the Lasag Topaz laser. The graph on the left illustrates the results obtained for a range of energy settings and the graph on the right illustrates the replicability of the lesions produced at a single energy setting.*

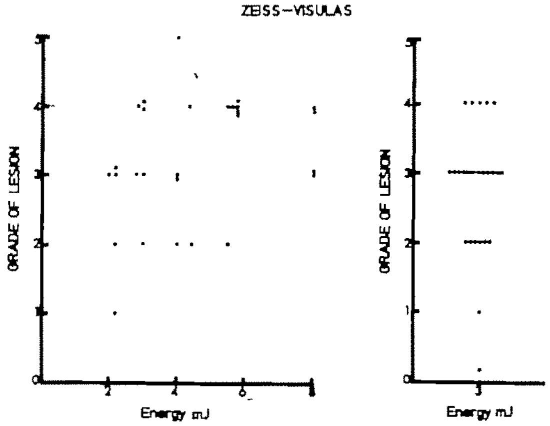

Fig. 3 *Graphs relating the grades of the lesion produced in the trabecular meshwork in relation to the laser energy applied with the Zeiss Visulas laser. The graph on the left illustrates the results obtained for a range of energy settings and the graph on the right illustrates the replicability of the lesions produced at a single energy setting.*

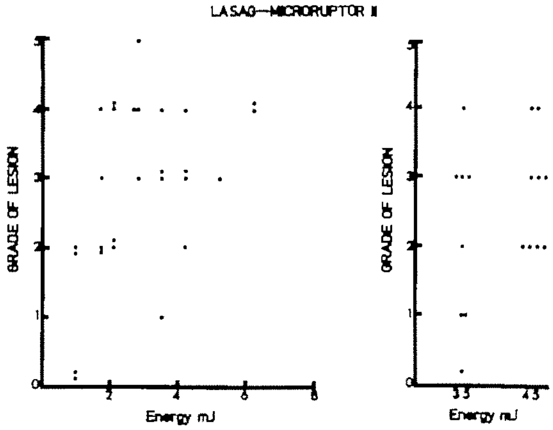

Fig. 5 *Graphs relating the grades of the lesion produced in the trabecular meshwork in relation to the laser energy applied with the Lasag Microruptor II The graph on the left illustrates the results obtained for a range of energy settings and the graph on the right illustrates the replicability of the lesions produced at two energy settings*

and 16° for Topaz and Microruptor II), and the transverse mode structure of the laser beam (low order mode for Visulas and Nanolas and TEM_{00} for Topaz and Microruptor II). All figures are from manufacturers' specifications.

Furthermore, the method of controlling the laser pulse energy may affect the stability of mode structure with respect to pulse energy. In both the Visulas and Nanolas equipment the laser source operates at a constant energy setting and the delivered output is varied by adjustable attenuators, while for the Topaz and Microruptor II the energy level of the laser itself is varied.

In practice, however, there seems to be little to choose between the four lasers. The tendency of the Microruptor II to produce grade 4 lesions with slightly lower pulse energy than the other instruments may result from the more pure mode structure giving a slightly better concentration of laser energy at the point of focus. This would cause more efficient plasma production and more effective tissue disruption. Although the Lasag Topaz is nominally similar in characteristics, the lesions produced with it do not show such an effect.

Clinical studies have indicated that reduction in intraocular pressure can be produced in patients with chronic open angle glaucoma by means of short-pulsed laser trabeculotomy.[1 10 11] However, the reduction in intraocular pressure may not be sustained, perhaps on account of healing which occludes the tiny fistulae. Neat fistulae into the canal of Schlemm which do not become occluded owing either to re-epithelialisation or to healing of the damaged outer wall of the canal would be the ideal goal. To this end the aiming criteria have recently been established[14] (the beam must be aimed at the posterior trabecular meshwork through the centre of the gonioscopic mirror), while the results described here suggest that pulse energies of between 3 and 5 mJ should be employed. A success rate of about 50% for the creation of a fistula into the canal of Schlemm might then be attained. Further experimental clinical studies are required to establish whether this technique is effective in practice.

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Efficacy of Nd-YAG laser iridotomies in acute angle closure glaucoma

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SUMMARY Between September 1984 and April 1987 a total of 150 patients underwent Nd-YAG laser iridotomy procedures at the Bristol Eye Hospital. Forty of these patients (27%) were treated for acute angle closure glaucoma (AACG), and three of them (7%) suffered recurrent AACG. Sixteen patients who had been treated for AACG have been challenged by a pharmacological provocative test introduced by Mapstone, with a total of 23 eyes being tested. A negative result was obtained in all cases. Provocative testing is recommended to help identify those at risk of recurrent AACG.

Laser iridotomy has gained widespread favour over surgical iridectomy because of factors such as avoidance of retrobulbar anaesthesia, maintenance of the anterior chamber, absence of risk of infective endophthalmitis, and application as an outpatient procedure. Nd-YAG is considered preferable over argon because of lower total energy requirements,[1] greater ease of iris penetration independent of iris colour,[2] and a lower incidence of iridotomy closure.[3-4] The long term safety of argon iridotomy compares favourably with that of surgery,[5] and initial concern about cataract formation with YAG iridotomy has not been confirmed.[6,7]

This study was undertaken to review the short term results of YAG laser iridotomies for AACG since its introduction in Bristol in 1984, and to assess the efficacy of iridotomies by provocative testing of a selected group of patients.

Material and methods

For the purposes of this study acute angle closure glaucoma (AACG) was defined as a red, painful eye, with elevated intraocular pressure in the presence of a closed anterior chamber angle. The case notes of all patients undergoing YAG iridotomies during September 1984 to April 1987 were reviewed. Sixteen patients were recalled for provocative testing, which was performed according to a technique developed by Mapstone.[8] Patients were selected on the basis of previous YAG iridotomy and no subsequent ocular hypotensive medications being required. One drop each of 10% phenylephrine and 2% pilocarpine was instilled into both eyes at 3-minute intervals for nine minutes after baseline intraocular pressures had been recorded by Goldmann applantation tonometry. Pressures were checked again at 1 hour, at which time the test was considered positive if a rise of 8 mmHg or greater had occurred. If negative at this stage, further drops were instilled if pupil size had not reached 3 mm diameter; otherwise pressures were checked again at 2 hours. The test was considered negative if the pressure had not risen by 8 mmHg by 2 hours. (Pupil diameter was measured by adjusting a focused slit beam on the Haag-Streit biomicroscope.)

Results

In the period studied 150 patients underwent one or more YAG laser iridotomies. Of these patients 40 (27%) were treated for acute angle closure glaucoma, 13 (9%) for subacute angle closure glaucoma, 44 (29%) for chronic glaucoma in which the anterior chamber angles were felt to be pathologically narrow, 17 (11%) for iris bombé (most often due to pseudophakia or posterior synechiae), 22 (15%) for prophylaxis on narrow angles, 3 (2%) for phacogenic glaucoma, and one after silicone oil insertion. Information could not be obtained on 10 patients (7%).

Of the 40 patients in the AACG group one has been lost to follow-up and one died in hospital, while the remaining 38 have been reviewed at intervals in

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Table 1 *Surgical procedures required (acute angle closure glaucoma)*

Treatment	*Acute eyes (n=38)*	*Fellow eyes (n=34)*
Single iridotomy	16 (42%)	28 (82%)
Two iridotomies*	10 (26%)	4 (12%)
Three iridotomies*	2 (6%)	0
Iridotomy(ies)+PI	4 (10%)	1
Iridotomy(ies)+trabeculectomy	6 (16%)	1

*At separate sittings PI=Peripheral iridectomy

Table 2 *Results of provocative testing**

	Zero hour		*2 Hours*	
	PD	*IOP*	*PD*	*IOP*
Acute eyes (n=15)	2·75 mm	15·4 mmHg	3·85 mm	14·3 mmHg
Follow eyes (n=14)	2·47 mm	15·3 mmHg	3·48 mm	13·3 mmHg

*Average values. PD=Pupil diameter. IOP=Intraocular pressure

the clinic and form the subject of this study. All patients had developed unilateral AACG, so 38 eyes with acute glaucoma were studied. Of the 38 fellow eyes, one eye had already undergone a trabeculectomy, one was rubeotic, and one was pseudophakic. Thirty-four fellow eyes were treated prophylactically. The average age of the patients was 74, and females predominated (75%). All patients studied were Caucasian.

A Lasag Neodynium YAG Series 2 Microruptor with CGI1 contact lens was used throughout. In Q switch and multimode, typical power settings were 5–10 mJ, and the number of pulses varied between 8 and 350. Of the 103 iridotomies carried out in total on the 38 patients studied, 20 were carried out by consultants, the remainder by junior medical staff, with a total of 15 different operators being involved (Table 1).

All but three of the patients studied were admitted to hospital for medical treatment prior to laser therapy. This involved the use of intravenous and oral acetozolamide (Diamox), and 4% pilocarpine eye drops, both of which were continued at least until the iridotomy. The interval between admission and laser varied from less than 12 hours to five days, with the highest IOP recorded at the time of iridotomy being 35 mmHg. Corneal oedema was recorded in five eyes with acute glaucoma at the time of iridotomy, and four of these required further YAG procedures. Bleeding from the iridotomy site was recorded in six eyes with acute glaucoma and one fellow eye, but in no case was the procedure abandoned. 70% of patients had a bilateral procedure carried out at the first sitting, with the remaining patients having the fellow eye treated at a later date. The average number of nights spent in hospital was five.

In nearly half of the eyes with acute onset a single iridotomy was successful, while the remaining eyes were treated again because the original iridotomy was judged to be too small or imperforate (Table 1). Four (10%) acute eyes went on to surgical peripheral iridectomy: on two eyes because the iridotomies were obviously imperforate, on one eye after recurrent AACG, and on the remaining eye because of persistently raised intraocular pressure despite a clinically patent iridotomy. Six (15%) eyes with acute glaucoma went on to trabeculectomy, in all cases because of persistently raised IOPs while on topical medications and with a clinically patent iridotomy.

Three eyes (7·5%) suffered recurrent AACG, at a maximum post-YAG interval of six weeks, and all had previously undergone more than one YAG iridotomy. The first eye was still receiving pilocarpine when the patient presented again, and the iridotomy looked patent. A trabeculectomy was carried out. The iridotomy of the second eye did not look patent, and a further iridotomy was performed. Iris bleeding occurred, and this iridotomy was also imperforate. Following a peripheral iridectomy the IOP became normal without any medications. The original iridotomy of the third eye was judged small at an early follow-up appointment, and the patient soon developed recurrent AACG. After a further YAG iridotomy the IOP was normal on no treatment.

Sixteen patients attended for provocative testing, with 16 acute and 15 fellow eyes being tested (Table 2). One patient did not stay for the required two hours, but was negative in both eyes at 1 hour. Three patients were still using pilocarpine, but all achieved the required pupil dilatation. In the 15 eyes with acute glaucoma the average pupil diameter rose from 2·75 mm to 3·85 mm at 2 hours, and the average IOP was 15·4 mmHg initially and 14·3 mmHg after two hours. In the 14 fellow eyes the average pupil diameter rose from 2·47 mm to 3·48 mm after two hours, and the average IOP changed from 15·3 mmHg to 13·3 mmHg. In none of the 29 eyes tested did the IOP rise more than 2 mmHg. In two eyes the maximum pupil diameter was 2·75 mm; all the other eyes achieved a pupil diameter of 3 mm or greater.

Discussion

Laser iridotomy has become an attractive alternative to surgical peripheral iridectomy in the treatment of AACG. One advantage of Nd-YAG over argon has been the smaller number of repeat iridotomies needed.[4] However, 48% of the eyes with acute glaucoma and 18% of fellow eyes required retreatment, well above the 9% quoted by Schwartz *et al.*,[2] but their group of 200 eyes included only 42 with AACG. Our figures indicate that eyes with acute onset are more difficult to treat, probably owing to factors such as corneal transparency and thickness, and iris oedema. In addition junior staff carried out most of our procedures and were probably on a 'learning curve'.[2]

The increased incidence of iris bleeding in acute eyes (16% compared to 3% in fellow eyes) is consistent with their engorged iris vasculature, yet the number is small compared with one reported study of 45%.[4] These eyes, however, were monitored for five minutes at the slit-lamp after the iridotomy, which was not the case in our study.

Analysis of the available clinical data did not reveal any factors that would be predictive of the number of laser procedures required. When those requiring only one procedure were compared with those needing more than one procedure, the average length of acute attack was found to be 2·6 days in the former and 1·82 in the latter. Similarly, presenting IOPs were almost identical in the two groups. Although iris colour was not analysed, previous studies have not shown darker irides to be more difficult to penetrate with the YAG laser.[11]

Nineteen eyes with acute glaucoma have required no further treatment after YAG iridotomy(ies). For this group the average IOP at presentation and the average length of acute attack were 57 mmHg and 3·3 days respectively. This compares with values of 55 mmHg and 2·8 days for the remaining 19 eyes with acute glaucoma requiring further medical or surgical treatment. These figures do not indicate that length of acute attack increases the risk of chronic angle closure glaucoma developing, and lend support to the policy of delaying iridotomy until IOP has been reduced.

Recurrent AACG does not appear to be a significant risk after surgical peripheral iridectomy,[9,10] but was an important complication after YAG iridotomy in our series. The three eyes that developed recurrent AACG had undergone more than iridotomy at the time of their first attack, but when they presented again it was clear in two that the iridotomy was imperforate. A further YAG iridotomy was carried out on one, and a peripheral iridectomy on the other, and neither of these eyes required further treatment. The third eye had a plateau iris configuration, and the patient presented again despite a clinically patent iridotomy. A trabeculectomy was carried out.

Closure of Nd-YAG iridotomies was not observed in one reported study[1] of 38 patients with acute or chronic angle closure glaucoma over a mean period of 15 months, patency being verified in these patients by direct inspection of the iridotomy site. A report of a larger series[2] of 200 Nd-YAG iridotomies describes two closures during a mean follow-up of 9·3 months, these occurring in patients with pre-existing chronic uveitis. It is likely that in one of our three recurrences the iridotomy was imperforate from the outset, but it is possible that in one patient the iridotomy closed later. This is well recognised with argon laser iridotomies.[1] The third eye developed recurrent AACG in the presence of a clinically patent iridotomy, an observation consistent with the diagnosis of plateau iris made at that time.

Clinical assessment of iridotomy patency may be made in a number of ways. Direct observation of the crystalline lens or vitreous through the iridotomy is certainly more reliable than iris retroillumination in this respect. The appearance of a plume of iris pigment issuing from the iridotomy site is a good indicator that the posterior iris pigment layer has been breached, but this phenomenon does not always occur during a successful iridotomy. Resolution of iris bombé, with deepening of the peripheral anterior chamber, should also occur but may be difficult to detect during the iridotomy procedure. Quigley emphasises that provocative testing should be performed on all patients who have had laser iridotomies after pupil block glaucoma, and he performed provocative testing as part of a follow-up on patients having argon iridotomies.[11]

The optimum size of a YAG laser iridotomy is not yet known, but gauging a minimum iridotomy size may be part of the learning curve mentioned earlier, going some way to explaining the recurrences in our patients.

Mapstone, using the technique described above, tested a group of 119 fellow eyes similar to ours[12] and found that 55% gave positive results after two hours. When further provocative measures were used and the test period was extended to five hours, this figure rose to 70%. During a mean follow-up of three years only one patient with a negative test result developed AACG. A negative result does not of course prove iridotomy patency, but a positive result indicates an inadequate iridotomy and the need for further treatment.

We consider that Nd-YAG iridotomies are a safe and effective treatment for AACG, but there is a small and significant risk of recurrence. Routine clinical methods may not identify those at risk, and therefore we advocate the routine use of Mapstone's test to help identify this group. We suggest that it be incorporated into the early follow-up of patients as soon as ocular hypotensive medications have been discontinued.

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Primary trabeculectomy in congenital glaucoma

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SUMMARY The reported success rates in the treatment of congenital glaucoma with goniotomy, trabeculotomy, and trabeculectomy suggest that trabeculectomy should be performed if the other procedures fail. We propose that the decision to perform primary trabeculectomy in primary and secondary congenital glaucoma reduces the effect which the many variable findings in surgical anatomy may have on the outcome of other procedures. This is a retrospective study of the results of primary trabeculectomy in 21 consecutive eyes of 15 patients with congenital glaucoma. Eighteen of 13 patients' eyes were controlled after a single trabeculectomy and remained controlled after a mean follow-up of 3·9 years (range 1·5 to 6·7 years). The role of primary trabeculectomy in congenital glaucoma merits further consideration.

Congenital glaucoma is a major cause of visual handicap in children and is responsible in some series for 2·5 to 10% of all children registered blind.[1] Its pathogenesis is disputed[2] but may be a variable embryological defect in the development of the anterior chamber[3] leading to glaucoma of all degrees of severity. The management of congenital glaucoma is primarily surgical, with goniotomy or trabeculotomy being the accepted procedures of choice.[4-7] While this treatment is effective, a delay in control of intraocular pressure is not uncommon, as patients regularly require more than one operation to achieve satisfactory intraocular pressure control.[2 7]

Some surgeons consider the results of primary trabeculectomy in children to be less satisfactory[1 8]: hence its general use as a secondary procedure when goniotomy or trabeculotomy are contraindicated or have failed. The purpose of this study was to evaluate the effectiveness of trabeculectomy as the primary procedure in 15 consecutive cases (21 eyes) of congenital glaucoma.

Patients and methods

Fifteen consecutive cases (21 eyes) of childhood glaucoma seen consecutively between 1980 and 1985 at our unit were studied. All observations were recorded by either one or both authors. The follow-up period after trabeculectomy ranged from 18 months to 6·7 years, mean 3·9 years.

The ocular family history, age of onset, and presenting signs and symptoms were collated. Corneal diameters, the cup-disc ratio, gonioscopy findings, refractive errors, the intraocular pressure, visual acuity, and ocular motility were recorded where possible before and after treatment. Visual acuities in patients too young for assessment of numerical values were extrapolated from oculomotor fixation patterns.[9] Anisometropia was defined as a spherical difference of ≥2·0 dioptres and/or a cylindrical difference of ≥1·50 dioptres. Horizontal corneal diameters were measured under general anaesthesia by means of Castroviejo calipers, and values greater than 10·5 mm at birth or 11·5 mm at 1 year were considered suspicious. Cup-disc ratios were evaluated by direct and indirect ophthalmoscopy where possible, and ratios of 0·3 or higher were considered suspicious. Cycloplegic refractions were performed and ocular motility was assessed by an orthoptist. Intraocular pressures were measured under general anaesthesia by means of a Perkins hand-held applanation tonometer and with the slit-lamp applanation tonometer when children were old enough to tolerate this technique. Intraocular pressures of ≤16 mmHg in the first year and <18 mmHg up to 3 years of age under general anaesthesia were considered normal[10 11] in the absence of other signs of overt disease or of disease progression.

All suspicious cases were initially examined under anaesthesia (EUA) and trabeculectomy done when

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Table 1 *Summary of age, operative procedures, intraocular pressure, and corneal diameter in group 1*

Case no	*Uni/ bilateral*	*Age (yr) at and type of surgery*	*Follow-up Postop (yr)*	*Intraocular pressure (mmHg)*						*Corneal diameter preop (mm)*	
				Preop		*1 month postop*		*Now*			
				R	*L*	*R*	*L*	*R*	*L*	*R*	*L*
1	B	0·4 R trab	2·2	26	26	5	5	10	10	13·5	13 5
		0·4 L trab.	2·2								
2	B	0·7 R trab	6·7	25	25	10	9	8	5	12·5	12·5
		0 7 L trab.									
3	B	0·3 R trab.	2·5	21	24	<10	<10	<10	<10	12·5	13·0
		0 3 L trab.	2·5								
4	U	0 6 L trab	1 5	11	28	12	10	15	12	11 0	12 5
5	B	0·5 R trab	2 7	18	18	12	10	10	10	12 5	13·0
		0·5 L trab	2 7								
6	U	2·2 L goniot.		18	36						
		12·2 L trab.	5·4	12	32	16	15	16	17	12 5	15 0
7	U	0·5 R trab.	6 3	25	12	12	12	12	13	12·0	10 5
8	U	0 9 L trab.	6 4	9	22	9	10	15	13	11 5	13·5
9	U	1 2 L trab.	5 4	13	30	13	8	14	10	11	13
10	B	0 8 L trab. R trab	2 4	20	20	13	10			14 5	14 5
		1 0 L goniot.† R+L trab R+L ccryo		13	18	13	10				
		2·1 L ccryo.‡	1 1	17	19			18	17	15 0	15 0§

*Trab.=trabeculectomy †Goniot =goniotomy ‡Ccryo.=cyclocryotherapy §Corneal diameter now

indicated. In bilateral cases the second eye was operated on at a second sitting, usually one week later. Serial EUAs were subsequently performed one- to four-monthy until the patient was old enough to tolerate a reliable outpatient assessment.

The anaesthesia was carried out by the same anaesthetist in the great majority of procedures. EUAs were performed with thiopentone induction and maintained with a combination of oxygen, nitrous oxide, and isofluorane. Trabeculectomy was performed following conversion to tracheal intubation using pancuronium and maintained by intermittent positive pressure ventilation and isofluorane.

One of us (RB) performed a trabeculectomy using a 6–7 mm limbal-based conjunctival flap followed by a 5 mm×5 mm shallow lamellar scleral flap. A 1mm×3mm trabeculectomy was performed with a slow controlled entry into the anterior chamber to prevent rapid loss of pressure, followed by a peripheral iridectomy. Viscoelastic material was used to deepen the anterior chamber in the last four cases. The lamellar scleral flap was resutured tightly with five 8-0 virgin silk sutures and the conjunctiva closed with a running 6-0 plain collagen or 6-0 Vicryl suture which included Tenon's capsule. In two of the early cases, where Schlemm's canal was identified at the anterior ends of the radial incisions, a trabeculotomy was also performed with the Harms double trabeculotomy probe.

The criteria for surgical success were stable or improved optic disc appearance, resolution of corneal oedema, lack of evidence of further corneal enlargement disproportionate to normal growth, stabilisation of refractive error, and average intraocular pressures (IOP) of 18 mmHg or less in the absence of other signs of decompensation.

Results

The 15 cases (10 males, five females) were divided into two groups. Group 1 had 10 patients (seven males, three females; 15 eyes) with primary infantile glaucoma and group 2 (glaucoma associated with congenital anomalies) consisted of five patients (six eyes), four with Sturge-Weber syndrome and one with Rubinstein-Taybi syndrome. The main presenting symptoms, listed by frequency, in group 1 were hazy cornea (seven cases), enlarged corneal diameter (five cases), photophobia (four cases), epiphora (three cases); whereas in group 2 three patients presented with an enlarged corneal diameter, one with a hazy cornea, and one case was referred for eye assessment because of Sturge-Weber syndrome.

In group 1 the intraocular pressure was normal in nine of 10 patients (13 of 15 eyes) on examination under anaesthesia one month after primary trabeculectomy (Table 1). This was associated with clearing of corneal oedema and reversal of optic disc cupping. From the outset none of these nine cases required any other form of intervention, after a mean follow-up of

Table 2 *Summary of age, operative procedures, intraocular pressure, and corneal diameter in group 2*

Case no	*Uni/ bilateral*	*Age (yr) at and type of surgery*	*Follow-up Postop (yr)*	*Intraocular pressure (mmHg)*						*Corneal diameter preop. (mm)*	
				Preop		*1 month postop*		*Now*			
				R	*L*	*R*	*L*	*R*	*L*	*R*	*L*
11	U	3·3 R trab	2 9	24	10	13	12	13	14	13	11·5
12	U	4·1 L trab	2 3	16	25	17	10	16	12	12	12·5
13	U	1 8 R trab/t-ot *	5·7	27	11	14	8	12	10	13	11·5
14	B	0·4 R trab	3 2	26	18	<10	<10	10	10	12 5	12 5
		L trab	3·2								
15	U	7 4 L trab.	3 3	16	26	14	16			12 5	12·5
		8·3 L trab/t-ot.*		18	32	16	22				
		9 5 L trab revision		16	30	15	20				
		10 4 L Yag laser	0·5	16	29			16	21		

*Trabeculectomy/trabeculotomy

4·1 years (range 1·5 to 6·7 years). One patient (case 10) required two trabeculectomies in each eye over four months followed by left goniotomy and later repeat cyclocryotherapy to both eyes. The intraocular pressure became normal for short periods in both eyes after each procedure but then gradually became decompensated. The intraocular pressure and other parameters remained stable one year after cyclocryotherapy. This case had severe disease at the initial operation (age 9 months) as shown by horizontal corneal diameter of 14·5 mm in each eye, gross corneal scarring, and gross distortion of limbal anatomy. An obvious Barkan's membrane was not seen in any of these 10 patients.

In group 2 the intraocular pressure was normal in four of five patients (five eyes) on examination under anaesthesia one month after primary trabeculectomy (Table 2). None of these eyes have since become decompensated after a mean follow-up of 3·5 years (range 2·3 to 5·7 years). One patient (case 15) with Sturge-Weber syndrome who was referred aged 7·3 years with left unilateral glaucoma proved difficult to control. This patient required four operations before satisfactory control was attained, which included a primary trabeculectomy, a trabeculectomy/trabeculotomy, trabeculectomy revision, and YAG laser division[12] of the fibrous bleb wall.

No immediate or late surgical complications were noted among the 18 eyes controlled after a single trabeculectomy except for a small hyphaema in three eyes, which cleared completely within three days of surgery. In particular, no patients developed scleral ectasia, staphyloma, or vitreous loss.[8] Two patients (cases 7 and 12) developed slight superior pupil peaking secondary to localised peripheral anterior synechiae between the iris periphery and the posterior edge of the draining fistula; however, aqueous outflow was clinically unimpaired. This complication occurred spontaneously in one case and developed in the other (case 7) following blunt trauma associated with a small hyphaema. There was documented reversal of optic-disc cupping (total or partial) in 10 of 11 eyes in whom media opacities did not preclude a view of the optic disc prior to surgery, while the cup-disc ratio of the 11th eye (case 6) was unchanged. The corneal diameters and refractive error of all 18 eyes stabilised; none became increasingly myopic on follow-up.

There were two patients (cases 10 and 15, three eyes) whose intraocular pressures were initially controlled after surgery but subsequently decompensated (case 10 within two months, case 15 after nine months). The cup-disc ratio, intraocular pressure, and refraction were stable after a total of 12 procedures to three eyes

The relative incidence of anisometropia, strabismus, and the final visual acuity was assessed for both groups of patients (Tables 3 and 4). In group 1 four of 10 patients had anisometropia, three of 10 patients had an exotropia, and 12 of 15 affected eyes had a visual acuity equivalent to 6/24 or better.

In group 2 three of five patients had anisometropia and three of five had strabismus (esotropia two cases, exotropia one case), while four of six affected eyes had a visual acuity equivalent to 6/24 or better. The visual acuity in one patient (case 12) was indeterminable owing to severe mental retardation.

Discussion

Of the 10 patients in group 1 nine (13 eyes) had control of IOP within one month of primary trabeculectomy and have not become decompensated after an average of 4·1 years (range 1·5 to 6·7 years). None of these nine patients suffered serious ocular complications, and all but one has a visual acuity equivalent to 6/24 or better, despite the presence of anisometropia in three, and strabismus in two cases

Table 3 *Summary of ocular findings in group 1*

Case no	*Uni/bilateral*	*Strabismus*	*Anisometropia*	*Haab striae*	*Visual acuity*	
					R	*L*
1	B			++	6/12	6/12
2	B			++	CSM	CSM*
3	B			++	6/12	6/12
4	U		+		CSM	CSM
5	B	+‡			CSM	CSM
6	U		+		6/5	6/9
7	U	+	+	+	6/24	6/6
8	U				6/6	6/6
9	U	+	+	+	6/6	4/60
10	B			++	UC US UM	UC US UM†

*CSM=central, steady, maintained †Uncentral, unsteady, unmaintained ‡Exophoria for near, exotropia for distance

(Table 3). Our good visual results can be attributed to the prompt optical correction of ametropia and anisometropia, and early control of intraocular pressure, as well as the vigorous treatment of potential ambylopia.[15]

It is generally acknowledged that the treatment of primary infantile glaucoma is surgical. The accepted procedures of choice are goniotomy provided there is a clear cornea and trabeculotomy ab externo for a hazy cornea.[1] It is generally considered that both procedures are comparable,[14] and success rates of 80% and over have been described.[4-7] However, surgical control with either technique warrants more than one procedure in a significant number of patients.[2,7] Trabeculectomy is not a first line procedure in primary infantile glaucoma, since it is claimed to be associated with a higher incidence of complications and a lower incidence of success in reducing the intraocular pressure to normal.[2,8] Beauchamp and Parks described an overall success of 50% in controlling IOP, which was reported as similar to previous experience.[8] Our surgical success rate of 87% after a single procedure is higher than most reported series on goniotomy or trabeculotomy. Rao and colleagues report a 75% success rate following primary trabeculectomy.[15] Our cases differed from those of Beauchamp and Parks in that all but one had trabeculectomy prior to 1·5 years old, whereas the patients in their series were generally older and hence more likely to have other ocular sequelae of buphthalmos, which may influence the outcome.[14]

There were five patients in group 2; four had Sturge-Weber syndrome and one had Rubinstein-Taybi syndrome. Of these patients four (five eyes) had a normal intraocular pressure within one month of trabeculectomy and have not become decompensated since then (mean follow-up 3·5 years; range 2·3 to 5·7 years). The visual acuity is better than or equivalent to 6/18 in these patients (case 12, indeterminable) despite the presence of anisometropia in two and strabismus in two (Table 4).

Glaucoma develops in 30% of patients with Sturge-Weber syndrome. It is unilateral in 90% of cases,[17] and the treatment is similar to that for other cases of congenital glaucoma except that goniotomy, the suggested primary surgical procedure, yields unsatisfactory results.[17] Our results with trabeculectomy were very encouraging and without complications, though numbers were small.

Apart from two patients (three eyes) in our series in whom trabeculectomy failed, complications were

Table 4 *Summary of ocular findings in group 2*

Case no	*Systemic diagnosis*	*Uni/bilateral*	*Strabismus*	*Anisometropia*	*Haab striae*	*Visual acuity*	
						R	*L*
11	Sturge-Weber syndrome	U		+		6/9	6/6
12	Sturge-Weber syndrome	U	+		+	*	*
13	Sturge-Weber syndrome	U				CSM	CSM
14	Rubinstein-Taybi syndrome	B	+	+	+	6/18	6/6
15	Sturge-Weber syndrome	U	+	+		6/6	6/9

*Indeterminable (severe mental retardation).

minimal. We share the view of Anderson[14] that the response to surgery in a given case is largely governed by the underlying nature of the case. In case 10 the symptoms dated back to the first weeks of life, but diagnosis was delayed, and the child presented at 9 months with permanent corneal scarring and horizontal corneal diameters of 14·5 mm and grossly distorted limbal anatomy. Case 15 presented with Sturge-Weber syndrome and developed a prominent bleb in contrast to the majority of our cases, which had a diffuse or slightly elevated bleb. It has been proposed that prominent bleb formation may be associated with an increased risk of late failure of trabeculectomy.[18]

Though maligned, primary trabeculectomy reduces the effect which the many variables in the anatomy of the anterior segment have on the outcome of other surgical procedures.[19] Eighteen of 21 eyes were surgically controlled after one procedure and have not relapsed. The gloomy picture of paediatric trabeculectomy surgery resulting in inadequate control of intraocular pressure and poor visual outcome has been refuted by our experience. We believe that the role of trabeculectomy as the primary surgical procedure, particularly in cases with primary congenital glaucoma, accompanied by vigorous treatment of potential ambylogenic factors merits further consideration.

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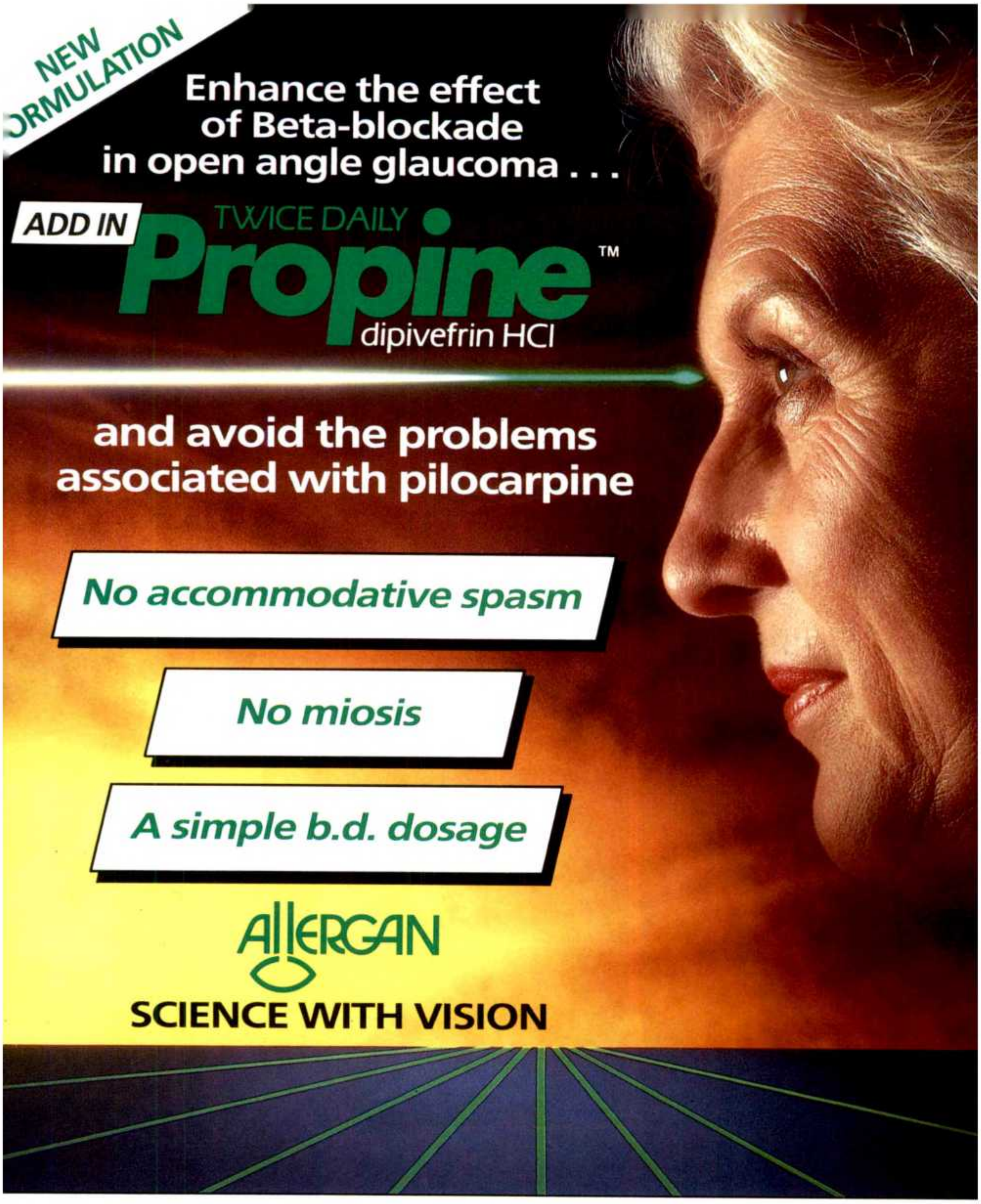

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British Journal of Ophthalmology, 1989, **73**, 191–196

Immune cells in a case of postherpetic marginal trophic ulcer

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SUMMARY The corneal surface was examined by means of replica histology, and the excised limbic conjunctiva was examined by routine histological and immunohistochemical methods with monoclonal antibodies directed against major histocompatibility class II antigens, lymphocyte subsets, Langerhans cells (HLA-DR, OKT_4-Leu3a, OKT_8, BA_1, B_1, and OKT_6) and immunoglobulins A, G, M, and D. The findings were compared with those found in normal conjunctiva. No inflammatory cells were present in the replica of the corneal surface. An inflammatory infiltrate composed of B lymphocytes and null cells, in addition to T lymphocytes, Langerhans cells, and polymorphs, was present in the epithelium as well as in the stroma of the limbic conjunctiva. The composition of the infiltrate points towards the involvement of cell mediated immunity as well as humoral immunity. No immunoglobulins were bound to the conjunctival epithelium.

After prolonged epithelial geographic ulceration or stromal herpetic involvement the surrounding epithelium may fail to grow over the epithelial defect even in the absence of active viral or secondary bacterial infection.[1] This failure produces indolent epithelial ulcers which may run a particularly prolonged course and do not respond to therapy with topical antiviral drugs. The ulcers are usually complicated by profound corneal anaesthesia, and herpes simplex virus cannot be recovered from the cornea.[2]

The precise pathogenesis of the trophic corneal ulcer is still not clear. According to Kaufman,[3] the failure of regrowth of the corneal epithelium is due to lack of epithelial basement membrane. Dohlman[4] on the other hand believes that the basic problem may be a mitotic arrest and inhibition of cell sliding at the edge of the epithelial defect. This would be related to the ratio of cyclic AMP and cyclic GMP in the cells. It has been suggested that collagenases and proteases secreted by the diseased epithelium and stroma perpetuate the corneal damage and that the use of collagenase inhibitors may reduce the secondary inflammation.[5] Moreover, idoxuridine is directly toxic to the epithelial cells and may be a contributing factor in the continued failure of the epithelium to cover the defects.[6]

Cell-mediated autoimmune phenomena have been reported in chronic herpetic keratitis with the demonstration of positive inhibition of leucocyte migration in response to corneal rather than viral antigens.[7] On the other hand Mondino *et al.*[8] suggested the involvement of humoral autoimmune phenomena in these cases owing to the finding of immunoglobulins and complement bound to the conjunctival epithelium adjacent to sites of active or previously active herpetic corneal disease. They detected circulating antibodies to the conjunctival epithelium in some cases and concluded that autoimmune phenomena may accompany or aggravate the extensive tissue destruction found in chronic herpetic keratitis.

The aim of this work is to study the cellular composition and distribution of the inflammatory infiltrate in a case of marginal postherpetic trophic ulcer in order to detect the role of immune mechanisms in the pathogenesis of trophic ulcers.

Subjects and methods

A 70-year-old female patient was followed up in the Department of Ophthalmology for a dendritic

Correspondence to Professor Dr L Missotten, Department of Ophthalmology, University Hospital St Rafael, Kapucijnenvoer 7, B 3000 Leuven, Belgium.

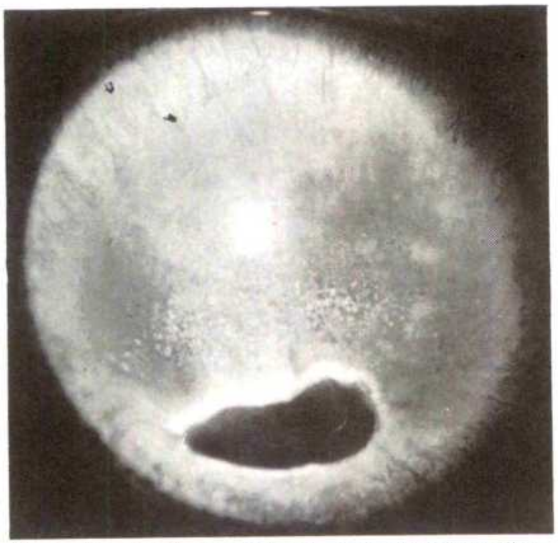

Fig. 1 *Trophic ulcer located at the cornea periphery. The ulcer is stained with fluorescein and seen through a cobalt blue filter.*

herpetic ulcer which progressed to marginal trophic ulcer (Fig. 1). She was treated with bromovinyl deoxyuridine (BVDU) and steroid eye drops in addition to an eyewash hourly with Ringer's lactate solution. This treatment remained unsuccessful.

A corneal replica was then made as described by Missotten and Maudgal.[9] The technique of making a corneal replica is as follows: (*a*) instill a local anaesthetic into the eye, (*b*) keep the eye open with a speculum and dry the corneal surface by blowing air, (*c*) apply a thin layer of collodion amyl acetate solution, 3%–4% w/v, on the corneal surface, (*d*) dry the solution by blowing air for about 2 minutes, and peel off the dried membrane with a fine curved forceps. This membrane is the replica of the corneal surface, which can be mounted on glass slides for microscopic study. The limbic conjunctiva adjacent to the ulcer was excised, and the ulcer area was cleaned under local anaesthesia.

The excised limbic conjunctiva was divided into two parts. One part was fixed in Bouin's solution and embedded in paraffin. Semiserial sections were cut and stained with haematoxylin and eosin for routine histology. The other part was frozen in liquid nitrogen-cooled isopentane and used for immunohistochemical study. Serial cryostat sections 5 μm thick were dried overnight at room temperature and subsequently fixed in absolute acetone for 10 minutes. An indirect immunoperoxidase procedure as described by Mason *et al.*[10] was applied for the following monoclonal antibodies: OKT_4, Leu 3a, OKT_8, B_1, BA_1, OKT_6, HLA-DR, and monoclonal antibodies directed against immunoglobulins A, G, M, and D.

The OK series of monoclonal antibodies were purchased from Ortho Pharmaceutical Co, Raritan, NJ, USA; Leu 3a, BA_1 and HLA-DR were obtained from Becton-Dickinson, Sunnyvale, CA, USA; B_1 was obtained from Coulter Electronic, Hialeah, FL, USA; monoclonal antibodies against immunoglobulins were obtained from Dakopatts a/s Denmark.

OKT_4 and Leu 3a define the helper/inducer T cell subset[11,12] and were applied simultaneously.[13] OKT_8 defines the suppressor/cytotoxic T-cell subset.[14] B_1 reacts with all mature B cells.[15] BA_1 defines mature B lymphocytes.[16] HLA-DR is directed against major histocompatibility (MHC) class II antigens.[17] And OKT_6 defines cortical thymocytes, epidermal Langerhans cells, and interdigitating reticular cells.[18,19]

Following incubation with peroxidase-conjugated rabbit antimouse Ig (Dakopatts a/s, Copenhagen, Denmark) the reaction product was developed in 3-amino-9-ethylcarbazole (Aldrich Co., Beerse, Belgium) and H_2O_2 according to Graham *et al.*[20] Sections were briefly counterstained with Mayer's haemalum and mounted in an aqueous medium.

A piece of normal conjunctiva obtained from a patient subjected to cataract surgery was studied in a similar way in order to correlate the findings observed in the case of trophic ulcer with those present in normal conjunctiva.

Results

REPLICA HISTOLOGY

The corneal replica was examined unstained by phase contrast and oblique illumination microscopy. The collodion membrane of the replica was then dissolved in acetone, and the cells removed with the replica were stained with Giemsa stain and examined by light microscopy.

The ulcer floor in the replica showed few necrosed cells, which were of irregular shape and arrangement. Some of them were fused. The ulcer margin was raised, forming a ridge sloping towards the floor (Fig. 2). It was formed of collections of degenerated cells, which were small, elongated, or rounded. These cells were partially fused and darkly stained. They had small, deformed dark nuclei. Many cells outside the ulcer area were swollen and some were fused. No inflammatory cells were seen in the surface layer.

NORMAL CONJUCTIVA

In the epithelium of the normal conjunctiva

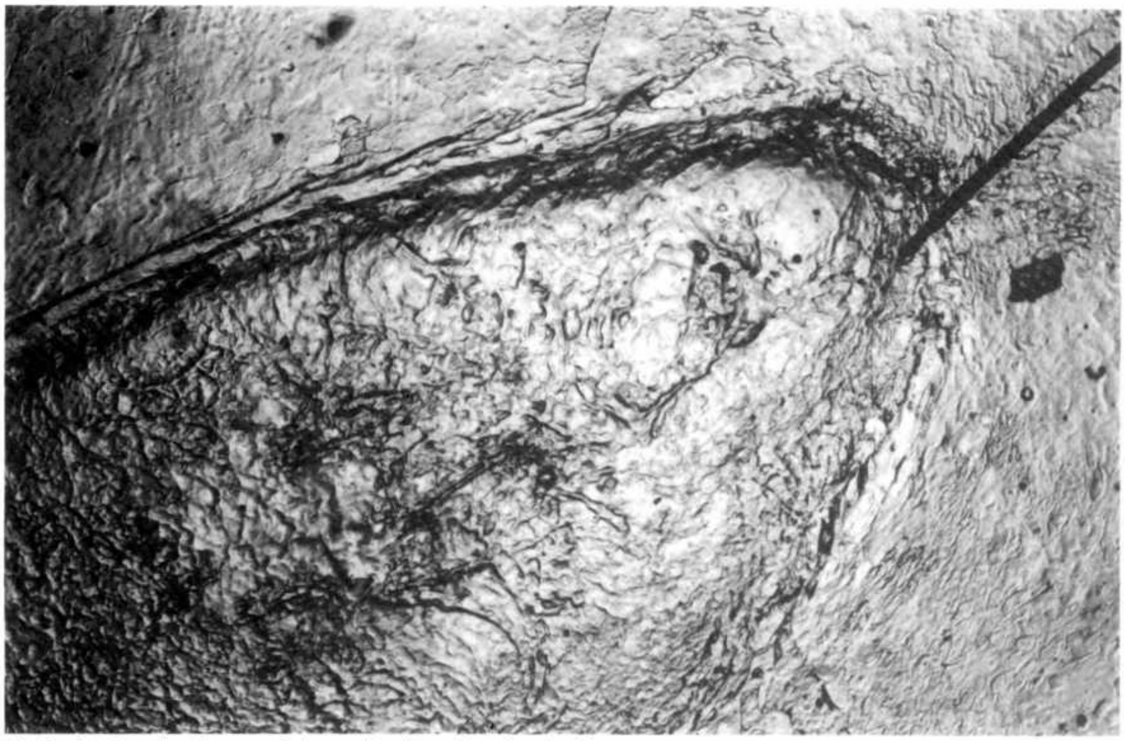

Fig. 2 *Replica showing part of the trophic ulcer. Note that the ulcer margin is raised over the surface and is sloping towards the floor of the ulcer. Oblique illumination microscopy, ×175.*

occasional irregular HLA-DR positive cells were present between the epithelial cells. Irregular OKT_6^+ cells were less numerous, and OKT_8^+ lymphocytes were rare. The substantia propria contained OKT_4-Leu $3a^+$, OKT_8^+, BA_1^+, and B_1^+ lymphocytes. In addition scattered irregular OKT_6^+ cells were found. The positive cells were present mainly in and around the blood vessels near the epithelium. Most of the round cells as well as the irregular cells were HLA-DR positive. The endothelial cells of the small blood vessels expressed HLA-DR. No immunoglobulins were expressed on the epithelial cells, but surface immunoglobulins, namely IgA, IgG, IgM, and IgD, were present on the surface membranes of some round cells in the stroma.

CONJUNCTIVAL BIOPSY OF THE TROPHIC ULCER

Routine microscopy shows the presence of an increased inflammatory cell infiltrate in the stroma as well as in the epithelium. The infiltrate is composed of neutrophilic polymorphs and of mononuclear cells (Fig. 3). In the epithelium the inflammatory cells are few and scattered. In the stroma the infiltrate is more intense and more diffuse.

Immunohistochemistry reveals a positive staining

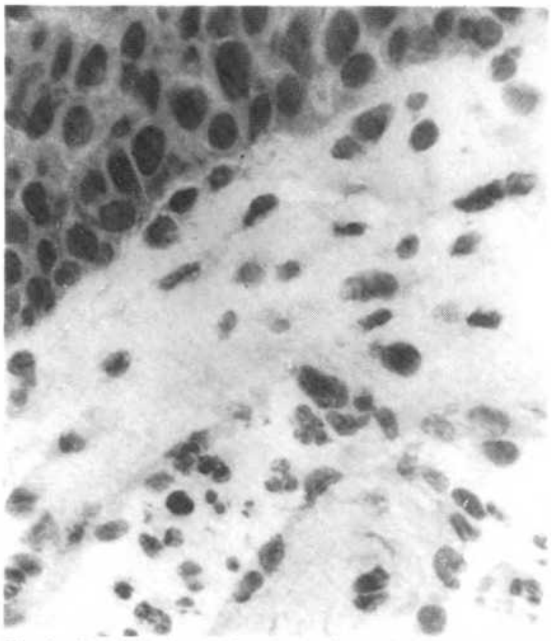

Fig. 3 *Mononuclear and polymorphonuclear leucocytic cellular infiltrate present in the conjunctiva adjacent to the trophic ulcer. H and E, ×540.*

Fig. 4 *Conjunctival biopsy of the trophic ulcer.* A: *the expression of MHC class II antigen on interepithelial cells which are either Langerhans cells or lymphocytes is demonstrated. Immunoperoxidase,* ×*800.*

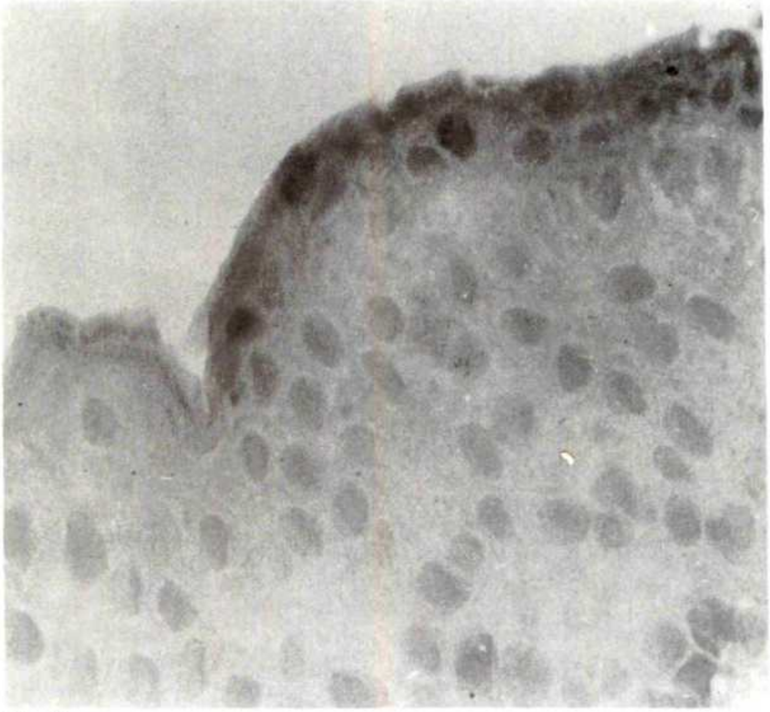

Fig. 4A

for HLA-DR on most of the inflammatory cells (Fig. 4A). The infiltrate is composed of OKT_6^+, OKT_4-Leu $3a^+$, OKT_8^+, BA_1^+, and B_1^+ cells (Fig. 4B). They are present in small numbers within the epithelium and in higher numbers in the substantia propria (Fig. 5). In addition many mononuclear cells not expressing any immunoreactivity with the monoclonal antibodies used in this study are observed. The

Fig. 4 B: *B_1^+, B lymphocytes in between the epithelial cells. Immunoperoxidase,* ×*800.*

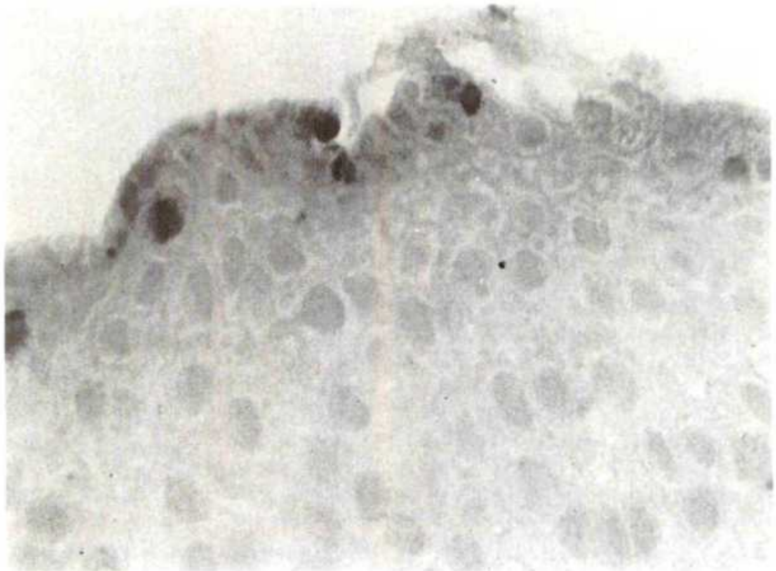

Fig.4B

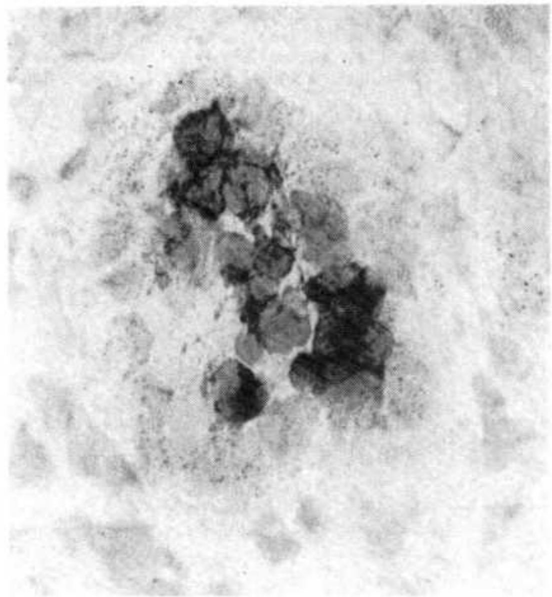

Fig. 5 *B$_1^+$, B lymphocytes present in the stroma of the conjunctiva adjacent to the trophic ulcer. Immunoperoxidase, ×800.*

conjunctival epithelium is not expressing immunoglobulins. Surface immunoglobulins, namely, IgA, IgG, IgM, and IgD, are found bound to the surface membranes of some mononuclear cells in the epithelium as well as in the substantia propria.

Discussion

From the replica histology it appears that there are no inflammatory cells in the surface layer of the trophic herpetic ulcer.

Routine microscopy of the conjunctiva adjacent to the ulcer shows an increased inflammatory infiltrate composed of mononuclear cells and polymorphonuclear leucocytes. The infiltrate is present in the epithelium and in the underlying stroma. Similar findings were noted in the conjunctiva adjacent to Mooren's ulcer,[21,22] and several studies suggested an autoimmune basis for the pathogenesis of this ulcer.[21,23,24]

Immunohistochemistry reveals many inflammatory cells expressing the major histocompatibility class II antigens. Class II histocompatibility antigens are known to be present on many types of cells involved in immune responses, including B cells, activated T cells, some macrophages, and interdigitating cells. Their presence on these cells is associated with antigen recognition and presentation to T cells and the initiation of specific B and T cell responses.[25,26]

In comparison with normal conjunctiva, the number of OKT$_6^+$, Langerhans cells, and of OKT$_8^+$, suppressor/cytotoxic T lymphocytes in the conjunctival epithelium near the trophic ulcer is increased. In addition OKT$_4$-Leu 3a$^+$, helper/inducer T lymphocytes and BA$_1^+$, B$_1^+$, B lymphocytes are present in the epithelium. In the substantia propria the inflammatory cell infiltrate is even more intense than in the epithelium. It is composed of a mixture of OKT$_6^+$, OKT$_4$-Leu 3a$^+$, OKT$_8^+$, B$_1^+$, and BA$_1^+$ cells. These cells are also more numerous than in normal conjunctiva.

The most striking observation is the presence of numerous round cells that are not stained with the monoclonal antibodies used and lack specific identifying surface markers for either T or B lymphocytes. Accordingly we suggest that many mononuclear cells present in the infiltrate are null cells. Because of their granular microscopic aspect some of these null cells are probably natural killer cells. In man natural killer cells have the appearance of large lymphocytes with an idented nucleus and prominent granules.[27] It has been shown experimentally that natural killer cells may have a role in limiting herpes simplex virus infections.[28]

No immunoglobulins are expressed on the conjunctival epithelial cells near the trophic ulcer. On the other hand Mondino *et al.*[8] detected immunoglobulins bound to the conjunctival epithelium in seven out of 11 patients with chronic herpetic keratitis.

Our findings indicate that an inflammatory reaction is present in the conjunctiva near the trophic ulcer. The inflammatory reaction is predominantly a reaction of mononuclear cells. The infiltrate is a mixture of accessory cells (Langerhans cells), various subtypes of T lymphocytes, B lymphocytes, and null cells. The presence of both T and B lymphocytes suggests an underlying immunological mechanism.

There are at least six antigenic glycoproteins at the surface of the virion that also appear at the surface of the infected cell.[29] Immune mechanisms can therefore interact not only with the virus but also with cells infected by the virus. This reaction is possible even in the absence of the replicating virus. We suggest that HSV-induced antigenic changes of the surface membranes of the epithelial cells stimulate immune reactions that lead to the development of a persistent ulceration.

The presence of Langerhans cells and T lymphocytes (helper/inducer and suppressor/cytotoxic subsets) as well as of B lymphocytes indicates that the underlying immune mechanisms are complex and that both cell mediated immunity and humoral immunity are involved. The presence of numerous null cells is more difficult to explain. It might be related to local steroid therapy, which is known to influence the immune response and the expression of antigens. But some of the unstained cells are probably natural killer cells and could be directly involved in the development of the ulcer.

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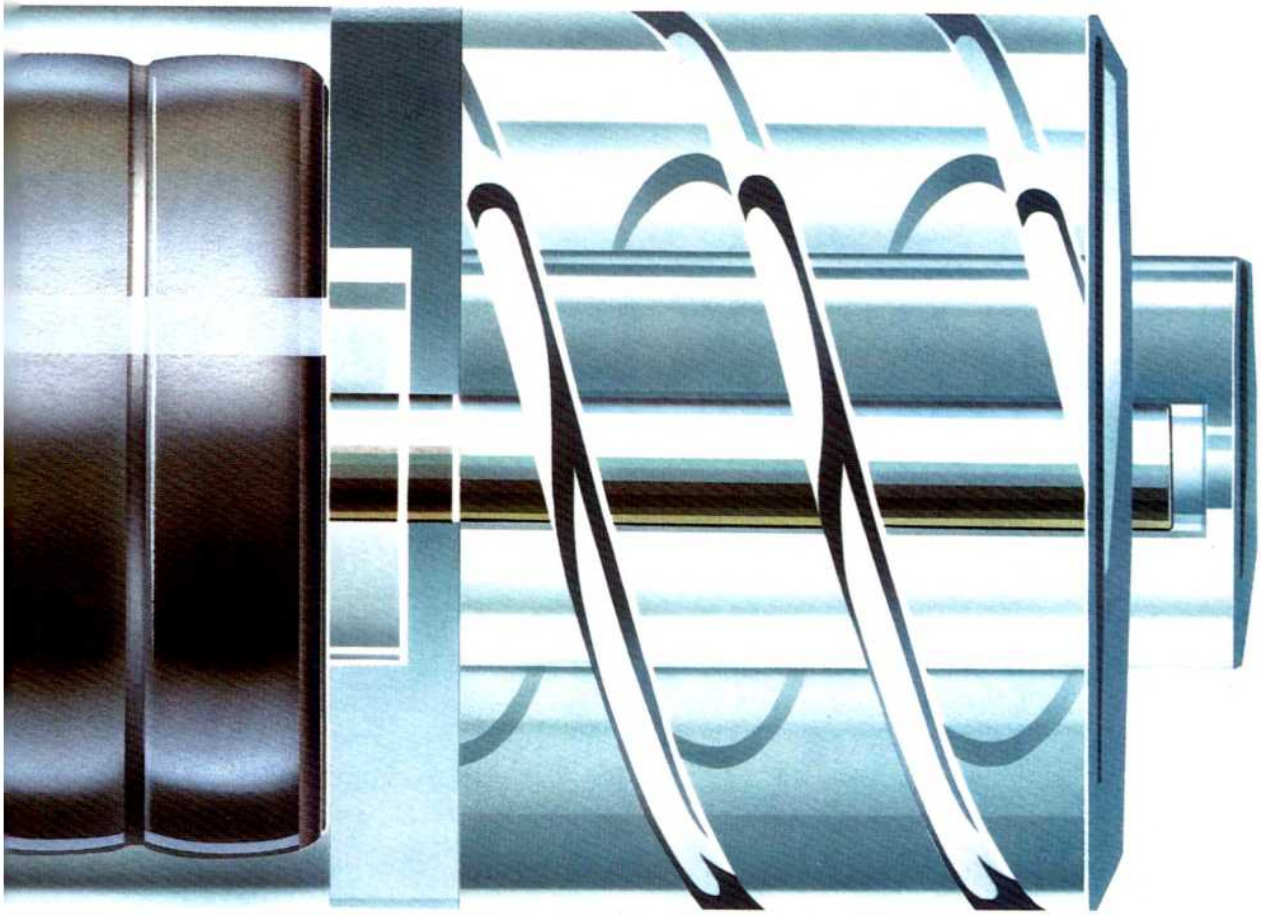

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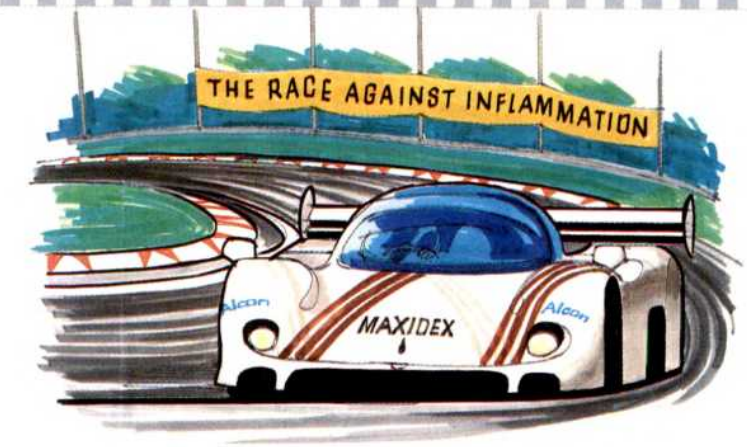

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SUMMARY A group of 20 patients (28 eyes) with proliferative retinopathy who required extensive argon laser photocoagulation to induce regression of new vessels is presented. The mean number of burns applied to each eye was 7225, with a maximum of 11 513. These were delivered in a mean of nine sessions over a mean period of 22·9 months. Twenty-five eyes (89%) had a final visual acuity of 6/18 or better. The remaining three eyes (11%) had severely reduced vision attributable to complications of proliferative diabetic retinopathy (traction retinal detachment involving the macula in two eyes and ischaemic maculopathy and a persistent vitreous haemorrhage in the third). Large amounts of confluent argon laser photocoagulation may be necessary for the elimination of new vessels in some patients, and it is our view that laser photocoagulation should be continued until regression of new vessels occurs. This is compatible with the retention of functional vision and good visual acuity.

Proliferative diabetic retinopathy is characterised by neovascularisation at the optic disc or in the peripheral retina. Recurrent vitreous haemorrhage and its sequelae and traction retinal detachment cause visual loss. It is the commonest cause of blindness between the ages of 30 and 65 years.[1] Several controlled trials have proved the benefit of photocoagulation in the treatment of proliferative diabetic retinopathy.[2-4] The largest of these was the Diabetic Retinopathy Study (DRS), which showed that a single session of photocoagulation reduced the incidence of severe visual loss (defined as a visual acuity of less than 5/200) in treated eyes.[2] The beneficial effect of photocoagulation is associated with the regression of retinopathy risk factors (RRF), particularly new vessels on the disc (NVD).[5] The question whether additional treatment is beneficial was not addressed by these trials, but it is widespread clinical practice to apply further laser photocoagulation until regression of new vessels occurs. How many burns can be applied? We present a group of 20 patients (28 eyes) who were included in the study because their disc new vessels required an excess of 5000 burns to induce regression, an end point which had not been achieved with lesser numbers of burns.

Patients and methods

The appointment records of patients attending the Diabetic Clinic at Moorfields Eye Hospital were analysed with the outpatient computer. The case notes of those attending regularly for treatment over the last year were examined. Patients who had received more than 5000 argon laser burns to at least one eye were identified. Patients who had further photocoagulation pending, or who had received xenon arc photocoagulation or direct treatment to disc new vessels, were excluded from the study. Information was extracted from the notes regarding age, duration of diabetes, treatment of diabetes, visual acuity, indication for photocoagulation, presence of maculopathy and its treatment, clarity of media, number of burns, number of treatment sessions, duration of treatment (defined as the time from the first to the last treatment session), and complications of photocoagulation and proliferative diabetic retinopathy.

Results

Twenty-eight eyes in 20 patients had received more than 5000 burns. Fifteen eyes were in 10 male

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patients and 13 eyes in 10 female patients. Eight patients (five male and three female) had received more than 5000 burns in both eyes. The mean age of the patients was 36·8 years, range 19 to 71 years. The mean duration since diagnosis of diabetes in the patients was 16·7 years, range 1 to 25 years. Twenty-three eyes were in 17 patients on insulin and five eyes were in three patients on oral hypoglycaemics. The indication of photocoagulation was new vessels on the disc (NVD) in all 28 eyes. Twenty eyes of 15 patients had new vessels both on the disc and elsewhere, and 17 eyes of 14 patients had some degree of vitreous haemorrhage at one or more stages before or during treatment. In all cases treatment was delivered by an argon laser through a Goldmann 3-mirror or a Rodenstock panfunduscopic contact lens. Spot size was 500 μm when using the Goldmann and 200 μm when using the Rodenstock contact lens with a duration of 0·1 to 0·2 s. The power level was adjusted to give slight blanching of the retinal pigment epithelium. The end point of treatment was complete regression of new vessels, or complete regression of vessels with gliosis, or residual fine, flat new vessels with fibrosis which remained static for at least six months.

Data on the number of burns, number of sessions, duration of treatment, and visual acuity is shown in Table 1. The mean total number of burns for the 28 eyes was 7255, range 5136 to 11513. The mean number of treatment sessions for each eye was nine, range three to 16, and the mean duration of treatment was 22·9 months, range five to 46 months. The mean interval between sessions was 12·4 weeks. The average of the mean burns per session was 854, range 395 to 1816. At completion of treatment 25 eyes of 20 patients (89% of eyes) had a visual acuity of 6/18 or better, and 16 eyes of 15 patients (57% of eyes) had 6/9 or better. Only three eyes of three patients (11% of eyes) had a final visual acuity of less than 6/18. The visual acuities before and after treatment are represented on the scattergram in Fig. 1.

Table 1 *Data on treatment and visual acuity*

Eye	*Total number of burns*	*Number of sessions*	*Mean burns per session*	*Duration of treatment (months)*	*Visual acuity Pre- Treatment*	*Visual acuity Post- Treatment*
1R	7871	9	875	5	6/9	6/18
1L	6380	15	425	28	6/12	CF
2R	5332	9	592	34	6/6	6/9
3R	10 327	10	1033	26	6/12	6/12
3L	9513	8	1189	15	6/9	PL
4R	7212	9	801	35	6/36	6/6
5R	5622	6	937	13	6/6	6/12
5L	7558	8	945	13	6/5	6/9
6L	7854	9	873	30	6/18	6/12
7R	7138	9	793	13	6/9	6/9
8R	5279	6	880	16	6/9	6/9
8L	5676	6	946	16	6/36	HM
9R	7835	15	522	32	6/6	6/9
9L	8897	16	556	32	6/9	6/12
10R	11 513	13	886	35	6/9	6/9
11L	5450	3	1816	5	6/5	6/9
12L	6817	6	1136	21	6/5	6/6
13R	8997	8	1125	28	6/9	6/6
13L	7963	10	796	34	6/9	6/18
14R	8705	10	870	32	6/9	6/18
14L	5136	13	395	34	6/5	6/9
15L	7882	8	985	12	6/12	6/9
16L	5674	11	516	16	6/9	6/12
17R	5530	9	614	9	6/9	6/9
18L	5858	9	651	14	6/36	6/12
19R	6200	7	886	24	6/9	6/9
19L	8068	8	1008	24	6/9	6/9
20R	6941	8	868	46	6/5	6/9

The complications of diabetic retinopathy and the degree of new vessel regression produced by photocoagulation are shown in Table 2. Ten eyes of six patients had focal (exudative) maculopathy, either before or during panretinal photocoagulation. Fourteen eyes of 10 patients had cystoid maculopathy. In five of these eyes (1R, 1L, 7R, 13L, and 18L) it was present before, and in the remaining nine eyes (3R, 5R, 5L, 6L, 9R, 9L, 14R, 14L, and 17R) it developed during panretinal photocoagulation. Nine of the 28 eyes received macular laser treatment. Eyes 1R and 1L had ischaemic maculopathy. Eyes 9R and 9L were aphakic. Three eyes (2R, 3L, and 6L) had rubeosis iridis, and this resolved after photocoagulation. Eye 4R had a superotemporal traction retinal detachment not involving the macula and had a final visual acuity of 6/6. Of the three eyes with final visual acuities less than 6/18, eyes 3L and 8L had a traction retinal detachment involving the macula and eye 1L had ischaemic maculopathy and a persistent vitreous haemorrhage. Eyes 3R and 8L also had persistent

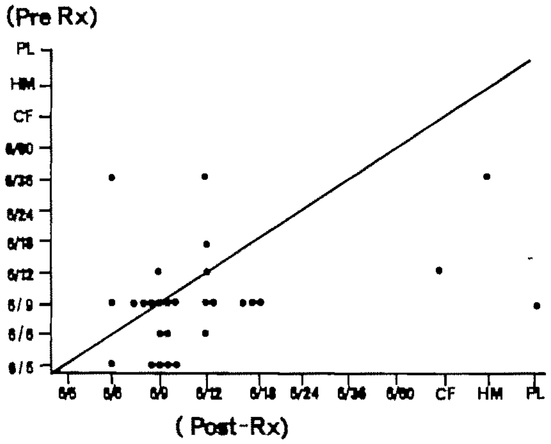

Fig. 1 *Scattergram showing visual acuities before and after treatment.*

Table 2 *Type of retinopathy and response to treatment*

	Maculopathy					*DNV regression*		
Eye	*Focal*	*Cystoid*	*Macular treatment*	*PNV*	*Vitreous haemorrhage*	*Complete*	*Gliosis*	*Residual*
1R	+	+	+	−	+	+		
1L	+	+	+	−	−			+
2R	−	−	−	−	+		+	
3R	−	+	−	+	−		+	
3L	−	−	−	+	+	+		
4R	−	−	−	+	+		+	
5R	+	+	+	+	−	+		
5L	+	+	−	+	−	+		
6L	−	+	−	+	+	+		
7R	−	+	−	+	+		+	
8R	+	−	−	+	+	+		
8L	+	−	−	+	+	+		
9R	−	+	−	+	+		+	
9L	−	+	−	+	+	+		
10R	−	−	−	+	+		+	
11L	−	−	−	−	−	+		
12L	−	−	−	+	−			
13R	+	−	+	−	−	+		
13L	+	+	+	+	+	+		
14R	−	+	+	+	+	+		
14L	+	+	+	+	−	+		
15L	−	−	−	−	−	+		
16L	−	−	−	+	+		+	
17R	−	+	+	+	+	+		
18L	+	+	+	+	+	+		
19R	−	−	−	−	−	+		
19L	−	−	−	−	−	+		
20R	−	−	−	+	−			+

PNV: peripheral new vessels. DNV: disc new vessels. Complete: complete regression of vessels. Gliosis: complete regression of vessels with gliosis. Residual: residual fine, flat new vessels with fibrosis which remained static for at least six months.

vitreous haemorrhage. One eye had transient shallowing of the anterior chamber without angle closure following photocoagulation. There were no inadvertently placed photocoagulation burns or their associated complications.

Complete regression of disc new vessels was the end result in 18 eyes of 13 patients (64% of eyes). In seven eyes of seven patients (25% of eyes) the disc new vessels regressed completely, but varying degrees of gliosis of the optic disc remained. In three eyes of three patients (11% of eyes) residual, fine, flat new vessels with fibrosis, which remained static for at least six months, were present on the surface of the optic disc.

Discussion

We have presented a group of patients in whom a large amount of argon laser photocoagulation over an extended period was required in order to induce regression of new vessels. The treatment protocol for argon laser photocoagulation in the DRS specified a single session of 800 to 1600 burns of 500 μm and 0·1 s duration, or 500 to 1000 burns of 100 μm.[4] This was shown to result in a lower incidence of severe visual

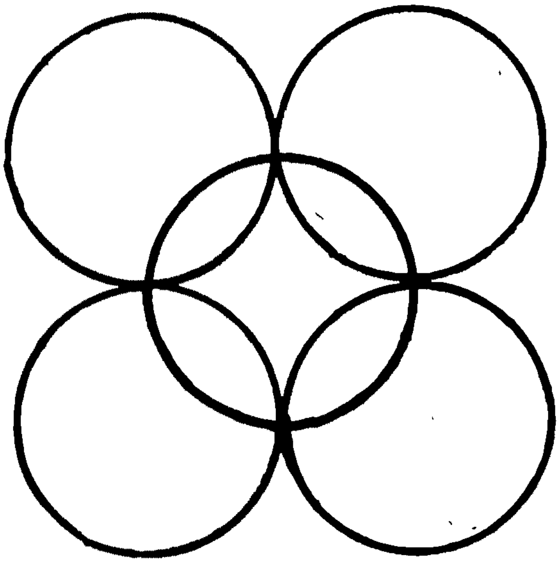

Fig. 2 *Diagram showing the necessity for overlap of circular burns to produce confluent treatment.*

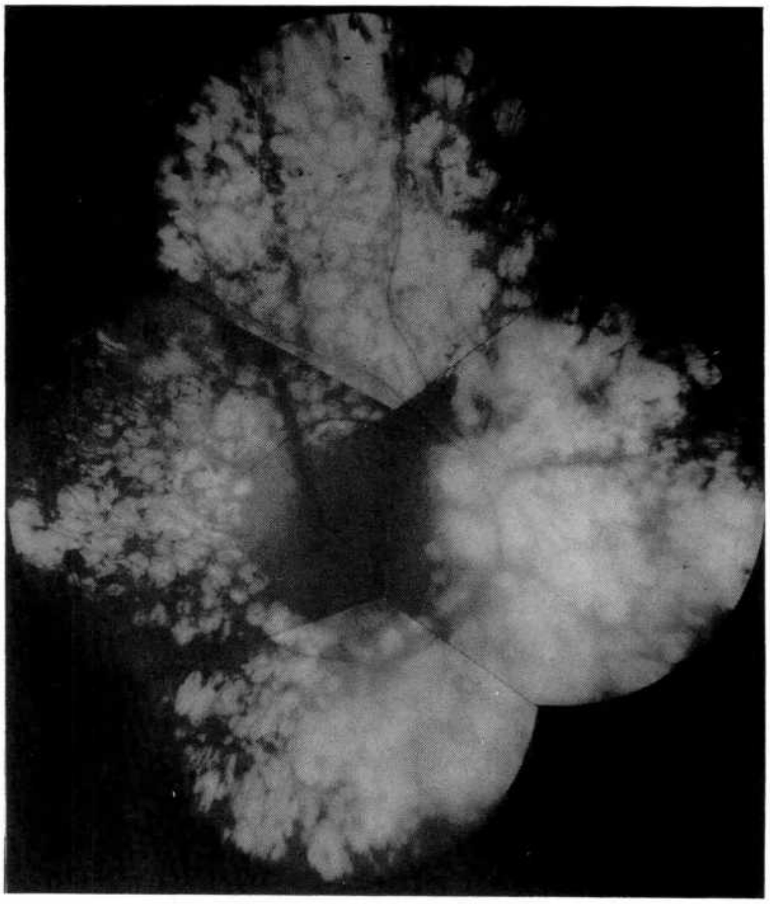

Fig. 3 *Fundus photography of eye 8R (5279 burns) illustrating confluent photocoagulation.*

loss (less than 5/200) at two years than the untreated control group. However, many treated eyes also lost vision, and, although unproved, it seems logical to apply further treatment in an effort to eliminate new vessels. Singerman and Weaver used 2000 to 3000 burns delivered in three or four sessions in a group of juvenile onset diabetics with proliferative retinopathy.[7] They concluded that the use of more extensive treatment reduced the risk of severe visual loss further than that achieved by the DRS. Little[8] allowed supplemental treatment in a group of 351 eyes with NVD. He applied a mean of 3181 burns in several sessions with good results. Vine reviewed 23 eyes with persistent new vessels following 3000 burns and found that regression occured in 12 of these eyes after a mean of 7550 burns.[9]

Given that additional panretinal photocoagulation is desirable, how should it be organised? It seems reasonable to allow time between sessions for regression to occur. In a prospective study of 50 eyes treated with a single session of 1200 argon laser burns according to the DRS protocol Doft and Blakenship found that eyes with no regression of retinopathy risk factors at 3 weeks had only a 36% chance of showing regression at 6 months.[10] They achieved some degree of regression of NVD in 86% of eyes at 3 weeks and in 82% at 6 months. This suggests that a decision regarding further treatment can be made reasonably soon after the initial session. In our group of patients the mean interval between treatment sessions was 12·4 weeks, which is probably longer than necessary. It is desirable to achieve regression of blood vessels as soon as possible owing to the risk of vitreous haemorrhage which can hamper further treatment. However, this must be balanced against other factors, including the tolerance of the patient and the increased incidence of transient complications such as exudative retinal detachment, choroidal detachment, and angle closure when many burns are applied in a single session.[11] Of these complications we experienced only one episode of marked shallowing of the anterior chamber without angle closure. The low occurrence of these complications in our patients may be a reflection of our lack of monitoring in the immediate post-treatment period as well as an indication of their practical significance. Transient complications aside, Doft and Blakenship found no major differences between a single session of 1200 burns and three sessions of 400 burns in the effect of treatment on visual acuity, visual field scores, or retinopathy risk factors.[11]

The cases we have presented represent a small minority of patients with proliferative diabetic retinopathy. However, their existence questions why some patients require such a disproportionate number of burns for regression to be induced. In Vine's study many patients had massive amounts of capillary closure on fluorescein angiography, and 50% of his patients had persistent new vessels even after an average of 7985 burns.[9] Hercules *et al.* observed that patients with the later stages of proliferative retinopathy respond less well to panretinal photocoagulation.[4]

The maximum number of contiguous but non-overlapping 500 μm argon laser burns that may be applied to a retina has been estimated as 5500.[12] All but four of the eyes in this study received in excess of 5500 and one (eye 10R) received more than twice this figure. There are several reasons why this should be. Firstly, the size of the histological lesion varies according to the exposure and may be smaller for lightly applied burns.[13] Secondly, the edge of a previous burn as seen through the contact lens and slit-lamp may not correspond to the limit of the area of histological damage. Thirdly, a large proportion of burns were applied overlapping previous burns. This is not necessarily undesirable and indeed is essential if a confluent area of treatment is to be achieved by means of circular burns (Fig. 2). A typical example of a retina which has received such extensive treatment is shown in Fig. 3.

Other factors which could affect the number of burns required to induce regression of new vessels include the presence of opacities in the media, the degree of choroidal pigmentation, variations in the energy density at the retinal surface,[14 15] the operators' accommodation, the astigmatism introduced by the contact lens, and the depth of focus of the system.[15]

Argon laser photocoagulation is associated with several adverse effects. These may be divided into complications, such as angle closure, macular oedema, and foveal burns, and inevitable side effects such as loss of visual field and colour discrimination.[16] Transient complications have already been discussed. Macular oedema occurred in nine of our patients following panretinal photocoagulation, but its development was not related to the total number of burns applied or to the mean number of burns per session, and all patients in this group had post-treatment visual acuities of 6/18 or better. It is unlikely that the patients presented here will have normal visual fields or colour vision, and this will form the subject of a further study. However, it is noteworthy that despite large amounts of photocoagulation they have retained functional vision with excellent visual acuity, 25 eyes (89%) having 6/18 or better.

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Rat bite injury to the eyelids in a 3-month-old child

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SUMMARY A 3-month-old child received severe rat bite injuries to the face, including subtotal loss of upper and lower lids of one eye. The presentation and management are discussed.

Animal bite injuries to the face are not uncommon and are most likely to be caused by dogs.[1] The lips, nose, or cheek are the commonest sites, though most ophthalmologists will have seen dog bites of the lids, often involving tears of the inferior canaliculous.[2] Rodent bites of the face are, however, rare in Great Britain. Rat bite injuries are sometimes seen in babies in some Third World countries, where the mother leaves the baby at the side of the field in which she is working (Laserna N, personal communication). This is the first case reported in Britain of a severe rat bite injury to the face, with consequent problems in management.

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Case report

A 3-month-old boy presented as an emergency in March 1985. His family lived in a country cottage in Gwent, South Wales. His mother had placed him in his cot in the morning while she attended to her older son downstairs. On hearing his cry she went upstairs and found him lying in his cot with severe lacerations to the left side of the face (Fig. 1).

The patient was promptly taken to the operating theatre, where extensive loss of lid tissue of the left eye was found. There was only a quarter of the normal tissue of both lids remaining laterally, the rest of the skin, tarsal plate, and tarsal conjunctiva having been removed. There were also three full-thickness

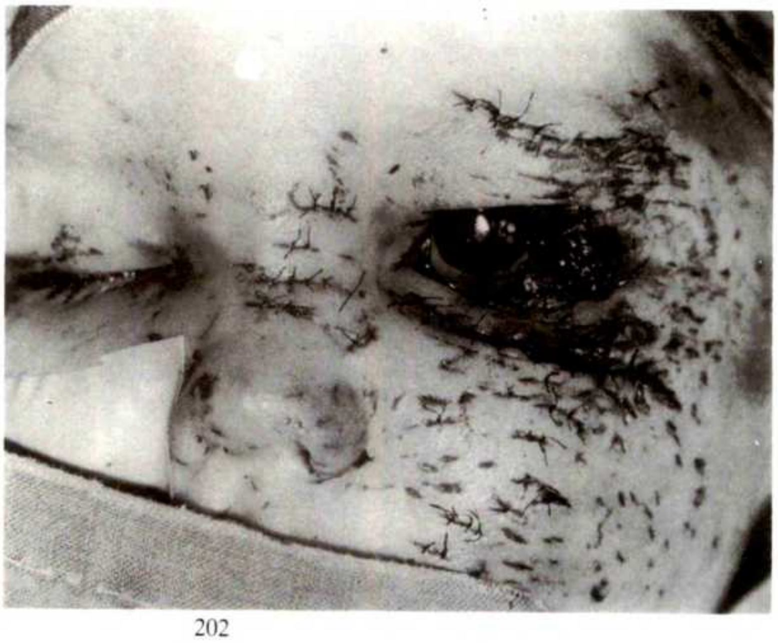

Fig. 1 *Facial injuries from rat bites, March 1985.*

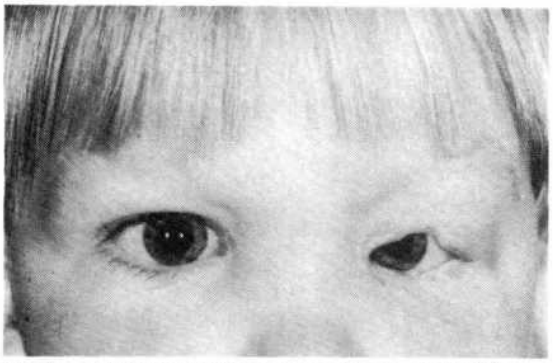

Fig. 2 *Appearance before cosmetic surgery, April 1986.*

lacerations below the left eye (repaired by the time the photograph was taken) and multiple wounds over the left side of face. The bulbar conjunctiva was damaged, but the globe itself was intact.

A plastic surgeon was involved from the start, as it was obvious that there would be long-term lid complications. The remnants of normal lid tissue were mobilised, and the conjunctiva used to cover the eye to prevent exposure of the cornea. A postauricular (Wolfe) graft was used to cover the eye completely. Despite the severity of the wounds, the baby did not develop any infection and was discharged a few days later.

The parents had originally thought that the injuries were due to a ferret which had been seen near the cottage. This was subsequently caught and killed, and the body, with photographs of the child's injuries, were sent to a forensic dentist at the School of Dentistry, Cardiff, who concluded that the injuries could not have been from a ferret but were almost certainly due to a rat.

By three weeks after the injury the Wolfe graft had sloughed and part of the cornea had become exposed, but was not ulcerated. Three months after the injury an examination under anaesthetic showed that adequate fornices had reformed, that the cornea was intact, and that it showed no staining with fluorescein.

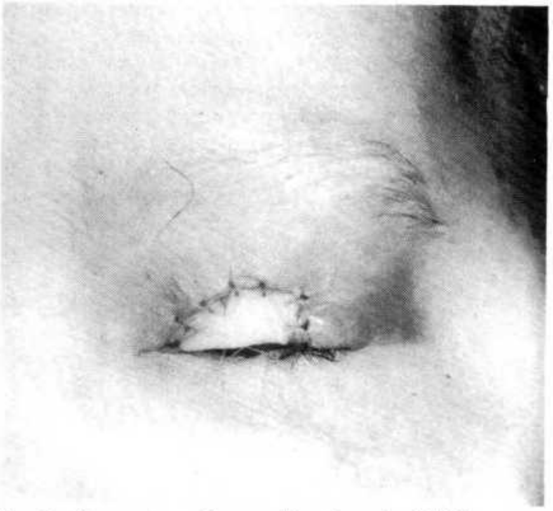

Fig. 3 *Composite graft sutured in place, April 1986.*

Five months after injury, at age 8 months, there was a marked left convergent squint with no response to the Catford-Oliver drum in that eye compared with a good response in the right eye. The left convergence was very variable. After five months of occlusion to the right eye the squint was still very variable and the left eye showed response to small toys.

Thirteen months after injury a composite graft from the left ear was performed to make good the vertical defect in the upper lid (Figs. 2, 3). This has improved the upper lid considerably, but the child still has some blepharophimosis, with some vertical and horizontal loss of tissue (Fig. 4). He has a residual dense left amblyopia, and further occlusion to the right eye is planned.

Discussion

This case report is unusual in both nature and severity. Rat bites may involve the face, particularly when the victim is sleeping, and orbital cellulitis due

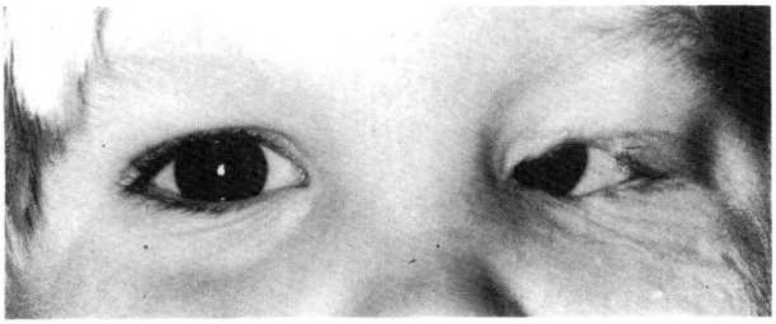

Fig. 4 *Cosmetic appearance, August 1986.*

to a rat bite has also been reported, but these reports, as well as that of injury to babies at the side of the field, all relate to Third World countries (Laserna N, personal communication).[3,4]

The severity of the injury and loss of tissue from both upper and lower lids presented a serious management problem. There was a considerable risk of exposure keratitis, and for this reason the eye was initially covered. However, after the loss of the Wolfe graft it was apparent that the fornices had quickly become re-established. The state of the lids has been improved by plastic surgery, but they are still far from normal. There is also the problem that the eye has inevitably become densely amblyopic, and further orthoptic treatment will be required to correct this.

The author thanks Mr M Y Khan and Mr A G Karseras for their assistance and advice, and the Medical Illustration Department, Royal Gwent Hospital

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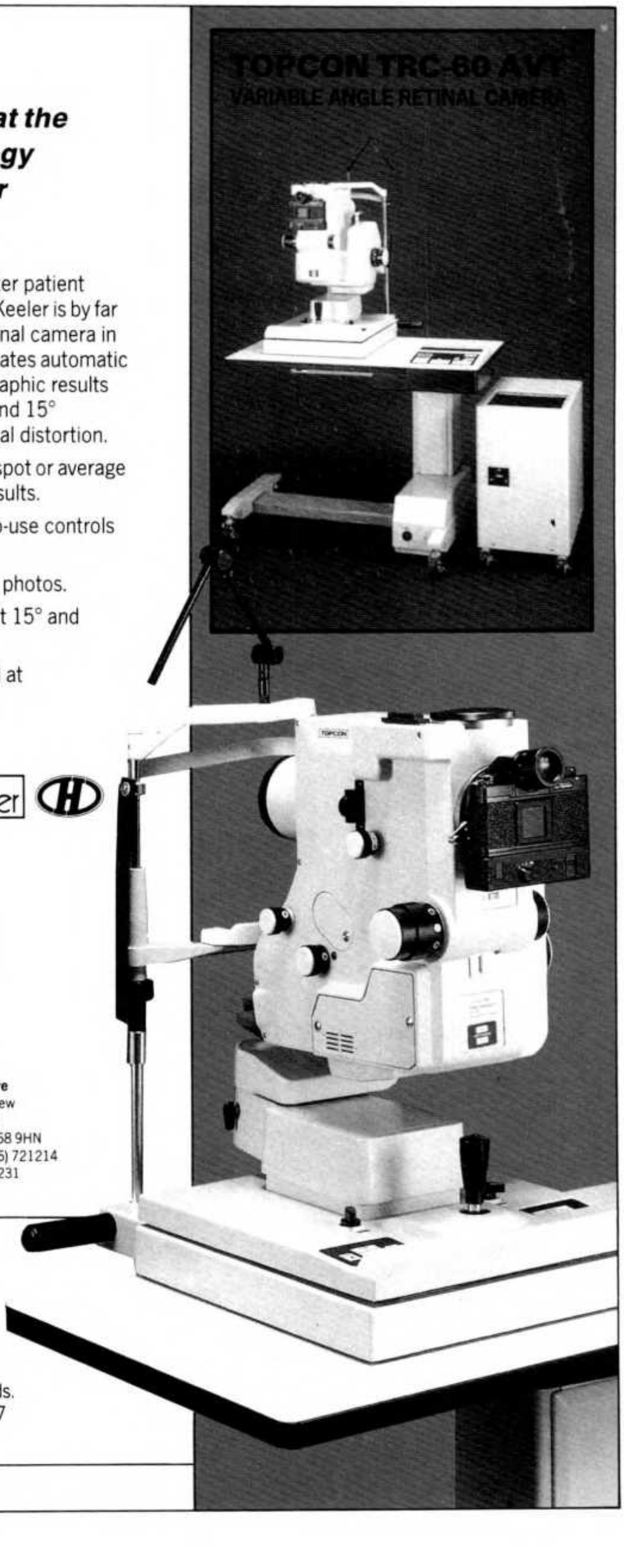

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Orbital cellulitis: review of 23 cases from Saudi Arabia

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SUMMARY We studied a total of 23 patients with orbital cellulitis and/or orbital abscess over a period of four years in Saudi Arabia. The study showed a high rate of abscess formation (12/23) and surgical intervention (17/23). Twelve out of 23 patients were 18 or more years of age. Furthermore, 12 of 23 (52%) patients had blind eyes on admission and remained blind after treatment, and one patient died of cavernous sinus thrombosis. Only 7/23 (30%) had a predisposing cause of primary sinus disease. This study of orbital cellulitis in a developing country presents a variation in disease pattern from previous reports and suggests that delay in the initiation of antibiotic therapy may lead to serious complications which may be life threatening. The course and outcome of orbital cellulitis may vary, depending on the predisposing factor, time of onset, associated systemic disease, or delay in initiation of treatment.

Orbital cellulitis is an ocular emergency that not only threatens vision but also can lead to life-threatening complications such as cavernous sinus thrombosis, meningitis, and brain abscess[1,2] In the management of orbital cellulitis physicians must recognise early signs and symptoms, be aware of predisposing conditions, and be prepared to administer prompt and appropriate therapy. Several recent reports[3-6] from different countries document similar clinical disease patterns in infectious orbital disease. However, this report highlights the serious outcome when therapy is delayed and therefore underscores the differences in the course and prognosis of the disease between a developing country and countries with well established and widely available medical facilities.

Materials and methods

Patients. A total of 23 patients with a diagnosis of orbital cellulitis without abscess and orbital cellulitis with orbital or subperiosteal abscess were admitted to the King Khaled Eye Specialist Hospital (KKESH) during the period of January 1983 to December 1986. We studied retrospectively the charts of patients who were admitted to the hospital with acute infectious orbital disease.

Clinical and radiological examinations. In all cases the cardinal signs of orbital cellulitis, including inflammatory proptosis or painful ophthalmoplegia, were present, indicating involvement behind the orbital septum. The diagnosis of orbital abscess was made when an abscess cavity was noted on computerised tomography scan or when pus was drained from the orbit or subperiosteal space at the time of surgery. All patients improved on the administration of appropriate antibiotics or surgical intervention. Radiological examinations were carried out in 20 of 23 patients and included CT scan in 16 of 23 patients and x-rays of the orbits and sinuses in 10 of 23 patients. One patient refused radiological examination, and two patients were not examined radiologically because they were known cases of endophthalmitis where the infection extended to the orbit.

Microbiological studies. Blood specimens and swabs from the periocular region and nasopharynx were obtained and cultured for bacteria and fungi. Specimens were cultured on blood agar (aerobic and anerobic conditions), chocolate agar, Sabouraud's agar, and thioglycolate Occasionally material was cultured on Lowenstein-Jensen medium to rule out tuberculosis, and an antimicrobial removal device (ARD) was used if an organism was not identified and the patient had been on a previous regimen of antibiotic therapy

Treatment. High dose intravenous broad spectrum antibiotics were given after cultures were obtained If an orbital abscess cavity was noted on CT scan or if the clinical situation deteriorated while appropriate

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antibiotics were being administered, the patient was subjected to surgical drainage of the abscess. Patients with primary sinus disease were generally given 24 to 48 hours to respond to antibiotic therapy before the sinus was drained.

Results

CLINICAL AND RADIOLOGIC FINDINGS

Of the 23 patients admitted for the treatment of orbital cellulitis or abscess 19 (83%) were male and 4 (17%) were female patients. The age range was 6 months to 66 years, with 12 (52%) aged 18 years or more and 11 (48%) under 18. There were 13 cases of orbital cellulitis with abscess formation and 10 of orbital cellulitis without abscess.

From the onset of symptoms until hospital admission and initiation of medical treatment there was a delay ranging from 2 to 40 days (mean 7·7 days). Delay among patients with orbital cellulitis and abscess formation ranged from 2 to 40 days (mean 9·4 days) and among those with orbital cellulitis without abscess formation from 3 to 12 days (mean 5·5 days).

PREDISPOSING FACTORS

A predisposing cause could be determined in 20/23 (87%) patients. Of these, seven were secondary to primary sinus disease, five to penetrating injury, four to endophthalmitis, two to previous surgery, and one each to acute dacryocystitis and rhabdomyosarcoma complicated by sinusitis (Table 1). Two of the patients who had sinus disease were immunosuppressed: one was diabetic and the other was receiving systemic corticosteroids. The patient who received systemic steroids had previously undergone splenectomy and eventually developed cavernous sinus thrombosis, brain abscess, and died.

Of the seven patients with primary sinusitis five were between the ages of 9 to 25, one was 48, and one was a 60 year old. An additional patient with sinusitis complicating rhabdomyosarcoma was aged 8. The ethmoid sinus was infected in all of the younger patients as well as in the 60-year-old. The 48-year-old was the only patient who had a primary focus of infection in the maxillary sinus. One patient with diabetes mellitus developed phycomycosis.

Four patients had been injured in motor vehicle accidents (aged 2, 5, 7, and 21 years) and a 4-year-old girl has suffered a penetrating injury with a knife.

Endophthalmitis caused orbital cellulitis as a result of a corneal ulcer in four patients. Two of the four had ulcers that were complications of previous surgical procedures. These four patients ranged in age from 40 to 66 years.

Table 1 *Predisposing factors for orbital cellulitis*

Factors	*No of cases*
Primary sinus disease	7
Penetrating injury	5
Endophthalmitis	4
Previous surgery	2
Dacryocystitis	1
Rhabdomyosarcoma	1
Undetermined	3
Total	23

MICROBIOLOGICAL RESULTS

Causative organisms could be identified in 17/23 (74%) of the patients. Positive cultures were obtained from an abscess site in the orbit or from an infected cornea or sinus. No positive blood cultures were obtained.

The organisms isolated included *Staphylococcus aureus* (8), *Streptococcus pneumoniae* (5), α-haemolytic streptococci (not *Streptococcus pneumoniae*) (3), and *Staphylococcus epidermidis* (1), *Haemophilus influenzae* (1), anaerobic streptococci (1), and a fungus of class Phycomycetes (1) (Table 2). Three of the patients had mixed infections, two of which followed trauma. Four patients had endophthalmitis leading to orbital cellulitis and this was caused by *Streptococcus pneumoniae* in two patients, *Staphylococcus aureus* in one patient, and *Haemophilus influenzae* in one. No patients had an anaerobic agent as the sole cause. Only one patient had fungal cellulitis, a 60-year-old poorly controlled diabetic, with an ethmoid sinus infection.

RADIOLOGICAL FINDINGS

Computerised tomography scans of the orbits and sinuses were obtained in 16 of 23 patients; the correlation between them and the clinical and surgical course was good. In two cases, however, an abscess cavity could not be diagnosed radiologically but was confirmed at surgery. Plain views of the orbit were taken in many of the patients who had a CT scan

Table 2 *Causative agents* in orbital cellulitis*

Agent	*No of patients*
Staphylococcus aureus	8
Streptococcus pneumoniae	5
α-haemolytic streptococci (not *Streptococcus pneumoniae*)	3
Staphylococcus epidermidis	1
Haemophilus influenzae	1
Anaerobic streptococci	1
Phycomycetes	1
Not cultured	6

*Three patients had mixed infections

Table 3 *Surgery performed for orbital infections*

Surgery	*No of procedures*
Drainage of orbital abscess	10
Drainage of sinus (ethmoid 6, maxillary 6, frontal 1)	7
Evisceration	4
Removal of infected supramid plate and glue	1
Total number of procedures performed on 17 patients	22

and also in 4/7 of the remaining patients, but in no instances were conventional radiographs of the orbit helpful in delineating abscess formation.

OUTCOME

All the patients were treated with intravenous antibiotics effective for both Gram-negative and Gram-positive organisms. Seventeen were subjected to surgery because of an orbital infection. Several of these had more than one operation either at one sitting or staged over the treatment period. The surgical interventions included drainage of an orbital abscess in 10 patients, drainage of a sinus or sinuses in seven, evisceration in four, and removal of an infected supramid plate and glue in one (Table 3) Twelve of 23 patients had blind eyes on admission and remained blind after treatment.

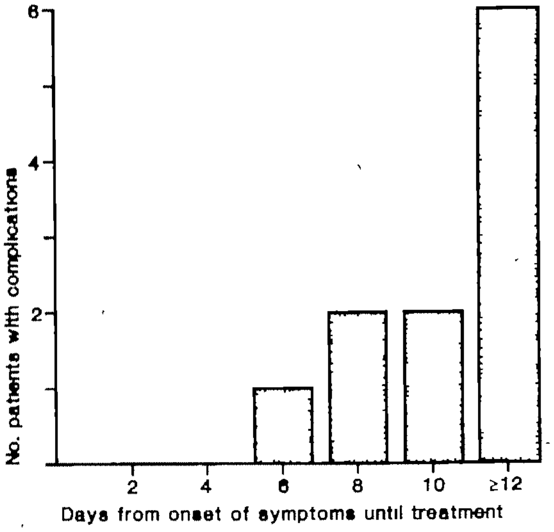
Apart from the decrease in vision and the surgical operations mentioned the following complications were noted in eight patients: one had an orbital haematoma postoperatively, two developed infected orbital plates with a fistula to the skin, two had recurrent orbital cellulitis due to undertreatment with antibiotics, two developed exposure keratitis, one extruded the acrylic spherical implant, and one developed large-angle exotropia after drainage of an abscess. In one patient there was spontaneous rupture of an abscess through the lid, and septic cavernous sinus thrombosis was observed in another, resulting in death. A progressive increase was noted in the number of complications, depending on how long the patient waited for admission and treatment after the symptoms or predisposing factors began (Fig. 1).

Discussion

The fact that only 23 patients in four years were identified with the diagnosis of orbital cellulitis with or without abscess formation suggests that many patients may be treated elsewhere. Some authors[2] require the presence of bacteria in the postseptal tissues for diagnosis, while others[10] require only inflammatory cells (sterile cellulitis) for diagnosis, with the bacteria being contained in the sinuses, globe, or lacrimal sac. Clearly it is often difficult to substantiate the actual penetration of bacteria into the soft tissues of the orbital cavity.

When a patient presents with infectious orbital disease, one may quickly conclude that orbital cellulitis is present because this is more frequently encountered than orbital abscess.[1-10] The incidence of abscess formation in orbital cellulitis varies from 0 to 25%.[1-10] In our series 13/23 (57%) developed orbital abscess; this is certainly greater than that reported in previous series and reflects a delayed diagnosis or treatment. In view of the fact that KKESH is a tertiary care facility, this also may indicate the bias in this highly selected sample of patients and may not reflect the true incidence of orbital abscess formation among patients with orbital cellulitis.

Because of the high incidence of abscess formation in this situation, management must be very aggressive. Management should include (1) obtaining adequate specimens for microbiological studies, (2) delivering high-dose intravenous antibiotic therapy immediately, (3) altering antibiotics according to sensitivities, and (4) intervening surgically at the proper time. If no organisms are seen by Gram stain, a β-lactamase resistant agent should be started until sensitivities are obtained. If the patient is less than 5 years of age, ampicillin or chloramphenicol should be added to cover for *Haemophilus* In patients with sinus disease 24 to 48 hours are usually allowed for a response to antibiotic therapy to occur before



3 patients had more than one complication

Fig 1 *Complications related to delay in treatment in orbital cellulitis*

surgical drainage of the sinus(es). An abscess cavity is considered a surgical emergency and should be drained promptly

Because of the high rate of abscess formation the number of patients undergoing surgery was also very large (73%). Previous studies[1-9] indicate a range of 0 to 38% of patients requiring surgery. Of the 13 patients in our study who developed orbital abscess 12 had surgery to drain the abscess (occasionally in conjunction with sinus drainage), and one orbital abscess spontaneously ruptured through the lid

The patient who died from cavernous sinus thrombosis had previous splenectomy following a motor vehicle accident and was maintained on steroid therapy

Few studies give an accurate age delineation of orbital cellulitis because most reports are from institutions that treat only children [1-5,7-8]

The CT scan was helpful in delineating the amount of involvement of disease process and indication for surgery. But in no cases were conventional radiographs of the orbit useful in delineating orbital abscess formation. In two cases, however, a CT scan could not define an orbital abscess suspected clinically and proved by surgical intervention Krohel *et al* have noted that an abscess developing over 24 to 38 hours may produce only non-specific inflammatory signs on CT scan and not identify an abscess [14]

This report draws attention to several differences in the presentation of orbital cellulitis and abscess formation in Saudi Arabia as compared with previously reported studies When confronted with patients in developing countries, one must bear in mind that the presentation of a disease may vary considerably from what has been reported previously.

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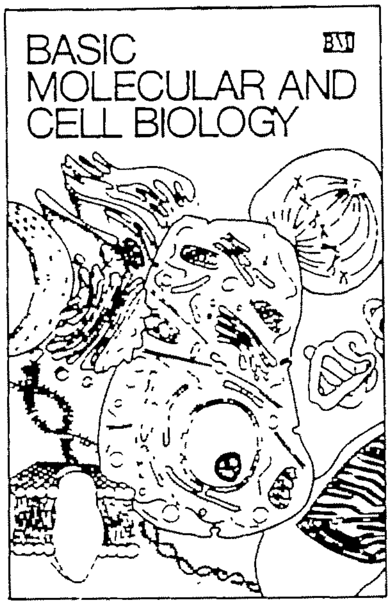

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Unfixed reference, monocular occlusion, and developmental dyslexia—a critique

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SUMMARY Stein and Fowler have proposed that poor binocular control of vergence eye movements is responsible for reading problems in a subset of dyslexic children, and that this subgroup is characterised by unstable performance on Dunlop's reference eye test. Four predictions from this hypothesis are evaluated in the light of published evidence. First, it is shown that a substantial minority of good readers have unfixed reference. Second, the evidence for a raised prevalence of unfixed reference in dyslexics is reviewed and contradictory findings are discussed. Third, it is argued that there is little support for the view that dyslexics with unfixed reference make different types of reading errors from those with fixed reference: indeed many dyslexics with unfixed reference have non-visual, phonological difficulties. Finally, it is argued that studies which claim that monocular occlusion is a successful treatment for 'visual dyslexia' are methodologically flawed and do not provide convincing evidence for this view.

It has long been recognised that low intelligence or lack of opportunity cannot explain all cases of difficulty in learning to read. Although there have been a number of cogent objections to the use of this label,[1] the term 'developmental dyslexia' remains popular, and will be used here to refer to severe reading problems not attributable to sensory or intellectual impairment or lack of opportunity. Many early writers thought developmental dyslexia resulted from an impairment in the visual perception of written words,[2,3] but research over the past 20 or 30 years has not supported this idea. Cognitive deficits are reliably found in dyslexic children, but these are verbal rather than perceptual, suggesting that the basis of the reading problem is difficulty in reliably classifying, remembering, and/or segmenting speech sounds.[4-6]

However, it may be mistaken to look for a single explanation for dyslexia. Reading involves a complex range of cognitive processes, and there may be several types of dyslexia, each arising for a different reason and for which different types of remedy would be appropriate. Attempts have been made to subclassify developmental dyslexia,[7-9] but there has been no consensus on a classification and no agreed criteria for distinguishing subtypes. Among those arguing for a distinction between dyslexic subtypes are Stein and Fowler,[10-12] who proposed that a subset of children with 'visual dyslexia' have abnormalities of visuomotor integration detectable by a 'reference eye' test developed by Dunlop *et al.*[13] They maintained that monocular occlusion helps stabilise performance on the Dunlop test and can lead to dramatic gains in reading ability of visual dyslexics. If these results are repeatable, then they are important in indicating an effective treatment for at least a subset of dyslexic children. However, a number of logical and methodological problems have been raised concerning this work.

Stein and Fowler: the theory

The claim made by Stein and Fowler is that unstable control of vergence eye movements with small targets is a sufficient, though not necessary, cause of reading difficulty. They regard 'unfixed reference' on the Dunlop test as an indicator of unstable vergence control. Four predictions follow from this:

(1) Children with unfixed reference will be poor readers.

(2) Not all poor readers will have unfixed reference, but there will be a raised prevalence of unfixed reference in dyslexic populations.

(3) Dyslexic children with unfixed reference

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will make reading errors characteristic of 'visual dyslexia', unlike other dyslexics who will be more likely to have linguistic deficits.

(4) Procedures which stabilise performance on the reference eye test will be effective treatment for visual dyslexia.

Origins of Dunlop's reference eye test

Dunlop *et al.*[13] described a new test which they regarded as a neurologically meaningful measure of eye dominance The subject views two slides (Clement Clarke fusion slides F69 and F70) simultaneously, one with each eye, in a synoptophore Each slide shows a house: one has a small tree on one side of the door, and the other has a large tree on the other side. When fusion is achieved, the subject sees a single house with a small tree on one side of the door and a large tree on the other, in the central 1° to 2° of the binocular field If angle of the slides is increased or decreased smoothly and slowly as the subject continues to fixate on the door, most subjects report that one of the trees moves before fusion breaks. The stable image specifies the 'reference eye'.

Dunlop *et al.* reported that dyslexia was associated with 'crossed reference', that is, discrepancy between reference eye and handedness. However, later workers noted that many children do not perform consistently on this test and so cannot be said to have a reference eye. It is this lack of stable reference, rather than crossed reference, that Stein and Fowler regard as associated with dyslexia. They reinterpret the neurophysiological significance of this test, regarding 'unfixed reference' as reflecting poor control of vergence eye movements to small targets.

Is there a link between unfixed reference and reading ability in normal populations?

Bishop *et al*[14] used the Dunlop test in a study of 147 8½-year-old children registered at a rural general practice. No relationship was found between crossed reference and dyslexia, but there was a significant association between reading attainment and *inconsistent* performance on the Dunlop test. The 44 (32·1%) children who did not give consistent responses to the test or who did not report movement of either tree ('unfixed reference') had a mean reading age 4·16 months below age level, whereas the 93 children with fixed reference (crossed or uncrossed) had a mean reading age 1·24 months above age level. However, those with unfixed reference had a lower mean IQ than those with fixed reference, and the difference in reading scores was no longer significant when IQ was used as a covariate. It was concluded that the association between reading attainment and unfixed reference arose because less intelligent children had difficulty in maintaining fixation and discriminating between small indicators.

Newman *et al.*[15] studied 323 children with a mean age of 8½ years, all of whom had WISC-R verbal and performance IQs of 90 or over. The orthoptist in this study was trained by Stein and Fowler to administer the Dunlop test, which was used to divide children into those with fixed reference (dominant eye on same side on eight or more out of 10 trials) or unfixed reference. Those with fixed reference (n=158) and unfixed reference (n=165) did not differ in age, mental age, or reading or spelling attainments

Stein *et al.*[16] gave the Dunlop test to 753 5- to 11-year old children attending normal primary school For 451 of these children reading test results were available. All had IQs above 90 on class-administered tests. There was a strong relationship between *age* and performance on the Dunlop test, with the proportion of children with stable reference increasing steadily from 52% in 5-year-olds to nearly 90% in 10-year-olds. Like Bishop *et al.* they found that around two-thirds of 8-year-olds had stable reference. Those 6- to 11-year-old children who had achieved stable reference were reading on average 6·3 months better than those who had not Data on IQ were not reported

Stein *et al.* argued that methodological differences were responsible for the failure of other studies to find an association between reading and Dunlop test performance, noting that considerable skill is necessary to obtain reliable results with the Dunlop test in children. However, there is an alternative explanation. Newman *et al.* analysed reading ages in relation to mental age, thus correcting for any IQ difference between children with fixed and unfixed reference Stein *et al.* did not. Bishop *et al.* found that when no correction was made for IQ there was a significant difference between those with fixed and those with unfixed reference. However, when correction was made for IQ this difference disappeared There is good evidence that both chronological and mental age affect performance on the Dunlop test, and it seems that results from all three studies can be explained in terms of these factors.

One point made by all three studies is that substantial numbers of normal readers have unfixed reference: for example, in the study by Stein *et al.* 24% of children whose reading was ahead of age level had unfixed reference on the Dunlop test. These findings pose a logical problem for any theory that maintains that lack of fixed reference on the Dunlop test is a sufficient cause of reading difficulties

Is there a link between Dunlop test performance and dyslexia?

Stein and Fowler[10,11] compared 80 dyslexics with 80 above average readers. Their mean age was just over 10 years. On the Dunlop test 63% of the dyslexics but only one normal child had unstable reference, a highly significant difference.

Stein and Fowler's 1985 study of 148 dyslexic children[12] did not include a normal control group, but their data may be compared with those of their normative study.[16] Stein (personal communication) confirms that the mean age of the dyslexic group was just over 9 years. In the normative study less than 20% of 9-year-olds had unstable reference, whereas this was found in nearly 70% of the dyslexics

This result is in striking contrast to those of Bishop *et al.* and Newman *et al.* One might wonder whether the discrepancy arises because of differences in study design: when the base rate of a disorder in a normal population is low, true associations may be difficult to detect because the number of disordered children is small For instance, if one estimates that dyslexia affects around 5% of children, then only about seven children in the study by Bishop *et al* would be affected, and an increased prevalence of unfixed reference might be difficult to detect in such a small sample. However, both Bishop *et al.* and Newman *et al.* did supplementary analyses of their data in which they selected from their samples those children with poor reading scores relative to intelligence. In neither case was there any suggestion of a higher rate of unfixed reference in this group. Nor was unfixed reference remarked upon by Dunlop *et al.*[15] in their original study of 15 dyslexics. Apart from work by Stein and his colleagues the only other study to find this association was by Bigelow and McKenzie,[17] who reported that nine out of 14 (64%) dyslexics had unstable performance on the Dunlop test, compared with only three members (21%) of a control group, composed of younger children matched on reading age.

If for the moment we ignore the negative findings and accept that a true association may exist between unfixed reference and dyslexia, we then have to consider what this might mean. One explanation is that visual problems cause dyslexia, but this is not the only possibility. There could be a causal link in the opposite direction, so that experience of reading affects performance on the Dunlop test. But this interpretation is difficult to reconcile with the data from Bigelow and McKenzie, and with a study by Stein *et al.*,[18] which showed that dyslexics were impaired on vergence eye movement control even when compared with younger normal children with whom they were matched on reading ability.

Another possibility is that unfixed reference may be a correlate of dyslexia without playing any causal part in reading problems There have been previous demonstrations of poor sensorimotor skills in children with specific developmental disorders, including dyslexia.[19–24] One interpretation is that motor immaturity and delayed language development are indicators of a single underlying cause—delay of neurological maturation.[25] An alternative, though not incompatible, interpretation is that attentional disorders associated with dyslexia disrupt performance on a range of tasks.[26] Unfixed reference could be regarded as a further example of this type of association, reflecting neurological immaturity and/or poor attention in dyslexic children.

Differences between dyslexics with fixed and unfixed reference

As well as finding a dramatic increase in the frequency of unfixed reference in their dyslexic group Stein and Fowler[10,11] reported that all the dyslexics with unfixed reference were 'visual dyslexics'. However, they gave no criteria for 'visual dyslexia', it is not clear who made this diagnosis (the two reports of this study differ on this point), and they did not state how many 'visual dyslexics' had fixed reference. Altogether the published account is too unclear for us to evaluate the claim that performance on the Dunlop test relates to type of dyslexia

Rather more detail is provided in the study by Stein and Fowler,[12] in which 148 dyslexic children were treated with monocular occlusion. Forty-five of these children had fixed reference when first assessed All children were seen by a reading specialist who 'arbitrarily categorised each child according to the predominant type of error he/she made when performing simple reading, writing, sequencing, rhyming, and alliteration tasks' Visual errors were defined as losing place on the page, having to point with a finger to keep the place, missequencing, and reversing and rotating letters and words when reading or writing. Phonemic errors involved failure to find rhymes or alliterations for 10 common words, and sequencing errors were failure to name the days of week or months of year (Note that the behaviours regarded as evidence of visually based reading problems are open to other interpretations.' It is unfortunate that no task of non-verbal visual discrimination or sequencing was included.)

The relationship between the classification of children as 'visual' or 'non-visual' dyslexics and performance on the Dunlop test was not reported Apparently this was because dyslexic children did not neatly subdivide into visual and non-visual types Many children made both 'visual' and 'auditory' errors. It is impossible to discover from the published account how error type related to unfixed reference, since these 'mixed dyslexics' were first excluded and only then were the remaining children compared on the basis of Dunlop test results.

If unfixed reference is an indication of a visual basis for dyslexia, then one would expect those with unfixed reference to have less evidence of early speech delay. However, dyslexics with fixed and unfixed reference did not differ in experience of speech therapy.

In order to accept that the Dunlop test distinguishes subtypes of dyslexic children, one would need to show that a blind, binary classification of dyslexics as 'visual' or 'non-visual' on the basis of reading errors predicted Dunlop test performance, and/or that children with unfixed reference made significantly more visual errors and significantly fewer non-visual errors than those with stable reference (*without* first excluding children who did not fit the hypothesis). Such analyses have not been reported. The data presented by Stein and Fowler[12] pose problems for their theory in demonstrating that many dyslexic children with unfixed reference have verbal difficulties that extend beyond reading.

Treatment of reading problems by monocular occlusion

The most important claim for a causal link between unfixed reference and reading problems is that dyslexic children with unfixed reference can be helped by monocular occlusion. This claim is made in the two studies of dyslexic children by Stein and Fowler described above.

In the first of these Stein and Fowler[10,11] studied 30 'visual dyslexics' who were asked to wear spectacles with the left lens occluded for all reading and close work. The attainments of these children were compared with those of 30 normal readers and 15 untreated visual dyslexics. After six months the reading age of the treated children had increased by an average of 13·5 months, compared with an increase of only 3·94 months in the untreated group: a statistically significant difference.

Unfortunately, the account of the study lacks details that would make a proper evaluation possible. We are not told the ages of the different groups of children, though it is evident from other studies that age is a crucial variable in determining Dunlop test performance. No details are given of the criteria for matching controls and dyslexics. The variance of reading scores in the treatment phase is not stated.

A further problem is that, as Stein and Fowler recognise, their result could reflect a placebo effect. Children and their parents and teachers were aware whether they were in a treatment or control group, and this could have affected outcome.

In 1985 Stein and Fowler[12] reported a study designed to overcome the methodological problems of their earlier work. 148 dyslexic children were randomly assigned to treatment and placebo groups. Those in the treatment group were given spectacles with one lens occluded, the remainder were given plain spectacles. After six months the children's reading was assessed, and the spectacles were removed from children whose reference remained or became fixed. All who still had unfixed reference continued to wear or were then given occluding spectacles to wear. After a further six months this procedure was repeated.

Monocular occlusion was significantly associated with development of fixed reference: this occurred in 51% of those treated with monocular occlusion and 24% of the placebo group. Furthermore, there was a significant difference in reading scores between children who established a reference eye during the course of the study and those who did not.

These data look impressive, but, as with the 1981–2 study, there are some methodological problems, and evaluation is hampered by omission of a number of important details, such as age, initial reading level, and IQ of the different groups. Data from one group of children (unfixed-occluded-unfixed-occluded-fixed) were not given, and it is often unclear how the data were analysed.

Further, Wilsher[27] pointed out that, although assignment of children to treatment was described as random, those with unfixed reference were much more likely to have been treated with occlusion. This suggests that the person assigning children to treatment groups believed in the efficacy of occlusion and was reluctant to deny children with unfixed reference the opportunity of treatment. Stein *et al.*[28] answered by stating that the imbalance arose because 53 children were lost from the study after the spectacles had been handed out. These children constitute a very high proportion of the study population, and one might ask why they were not mentioned in the original paper. This seems especially surprising, since the authors described another 53 children who did not participate in the study, 24 because they were not dyslexic, 9 with ophthalmological conditions, and 20 who failed to return for follow-up. This sort of omission not only weakens one's confidence in the report of this study, it also introduces a worrying possibility of bias. If there was a marked difference between treated and placebo groups in the frequency of drop-outs, then this suggests that parents and children were not blind to treatment status. Stein *et al.* suggest that it was the lack of improvement associated with placebo rather than awareness of

Table 1 *Outcome data after the first six months*

	UNU	*UNF*	*UOU*	*UOF*	*FNF*	*FOF**
n=	*28*	*11*	*28*	*31*	*29*	*17*
Age (months)						
Mean	111·0	118·2	110·0	113·6	111·3	112·7
SD	12·14	15·54	15·63	17·59	12·83	13·13
Initial reading age						
Mean	79·9	83·5	80·8	88·5	83·0	79·6
SD	10·13	9·49	9·99	10·65	8·16	8·88
Reading T score† (initial)						
Mean	34·1	34·0	34·7	38·5	35·3	33·4
SD	4·61	3·52	4·17	5·80	4·25	3·74
Matrices T score						
Mean	46·1	44·4	47·8	47·9	48·5	44·9
SD	8·32	6·59	6·21	10·15	9·62	8·61
Similarities T score						
Mean	50·8	47·9	50·4	53·9	49·5	47·8
SD	7·57	9·21	8·36	7·79	7·14	8·11
Reading age gain (months)						
Mean	5·6	7·1	5·7	11·6	8·8	6·8
SD	4·71	7·70	6·81	9·94	8·18	5·06

*Dunlop test coding: F=fixed reference (stable vergence); U=unfixed reference (unstable vergence)
Treatment coding O=occluded, N=placebo or untreated.
†T score is a standard score with mean 50 and SD 10.
Reading T scores derived from reading ages provided by Dr Stein

being in a placebo group that caused children to drop out, but if that were the explanation, then more children with fixed reference should have dropped out, as they too were making poor progress.

In response to requests for further details about this study, Dr Stein kindly agreed to provide the raw data for reanalysis to investigate how far variables such as intelligence, age, and initial reading level may have affected gains in reading age. The data from the first six months of the study are summarised in Table 1. There are some discrepancies between the data given here and those reported in the *Lancet.*[12] In particular, the standard errors in the published account are much smaller than those derived from standard deviations shown here. Dr Stein has confirmed that this arose through computational error and the figures given here are the correct ones.

The prediction from Stein and Fowler's theory is not that occlusion will be effective for everyone, but rather that its efficacy will depend on initial status. Thus if children are divided on the basis of initial status (fixed (F) or unfixed (U) reference) and treatment (occluded (O) or placebo (N)) the prediction is that there will be an interaction, so that treatment has a significant effect only on the initially unfixed group. When data for gain in reading age are analysed in a two-way analysis of variance neither main effect is significant (F ratios less than 1), and nor is the interaction ($F(1, 140)=2{\cdot}92$). A supplementary analysis just on children who did not initially have stable reference also gives a non-significant difference between treated and untreated groups ($F(1, 96)=2{\cdot}9$). Thus we cannot reject the null hypothesis that treatment has no effect on reading.

Nevertheless, on the basis of a different type of analysis, Stein and Fowler argue that their results do support the theory. It seems reasonable to suppose that occlusion would improve reading scores only if it brings about fixed reference. Stein and Fowler therefore subdivided both treated and untreated groups of children according to whether stable reference was achieved after six months. When this is done, significant differences in reading age gains can be shown between groups. If the six groups shown in Table 1 are compared on reading age gain in a one-way analysis of variance, a significant main effect is found ($F(5, 138)=2{\cdot}71$; $p<0{\cdot}05$). If groups UOU and UNU are combined and compared with groups UOF and UNF a significant difference in reading age gain is found ($t(96)=3{\cdot}06$; $p<0{\cdot}01$), though there is no significant difference between UOF+UNF versus FOF+FNF ($t(86)=1{\cdot}29$, NS). It is on the basis of this result that Stein and Fowler maintain that attainment of stable vergence eye movements facilitates reading development.

As Wilsher[27] noted, there are problems with this analysis. In dividing subjects by reference eye status at follow-up, one has moved from classification in terms of an independent variable over which there is experimental control to classification in terms of a dependent variable. This makes interpretation of results ambiguous: performance on the Dunlop test at follow-up may relate to reading outcome, but we cannot be certain of the direction of causality, or indeed that any causal relationship is implicated. Other factors, discussed above, such as influence of reading experience on Dunlop test performance, could be responsible for this relationship. Alternatively, some third variable, such as rate of maturation, might affect both stability of reference eye and reading ability without the two being directly causally related.

Scrutiny of the data presented in Table 1 suggests that this latter interpretation may be the correct one, and that initial reading status might be a crucial variable determining outcome. When *initial* reading ages of all six groups are compared in a one way analysis of variance, a significant main effect is found ($F(5, 138)=3{\cdot}31$; $p<0{\cdot}01$), and a specific comparison between groups UOU+UNU vs UOF+UNF with a t test shows a significant difference in favour of those with fixed reference at follow-up ($t(96)=3{\cdot}3$; $p<0{\cdot}01$). Thus those groups that show most gain in reading ability over the first six months also start off with higher reading ages. An analysis of covariance was carried out to compare reading age gain scores

Table 2 *Outcome data after 12 months.*

	UNUOU	*UNUOF*	*UNFNF*	*UOUOU*	*UOUOF*	*UOFNF*	*FNFNF*	*FOFNF*
n=	*8*	*20*	*11*	*14*	*14*	*31*	*29*	*17*
Reading T score (initial)								
Mean	35·5	33·6	34·0	34·1	35·4	38·6	35·3	33·4
SD	5·45	4·26	3·52	5·27	2·73	5·81	4·26	3·74
Reading age gain (from 6th to 12th month)								
Mean	5·9	9·7	12·4	6·3	8·6	10·4	4·6	9·4
SD	6·27	8·55	15·25	8·61	6·30	11·05	7·99	17·56
Reading age gain (whole 12 month period)								
Mean	10·6	15·6	19·5	11·4	14·9	21·9	13·4	16·1
SD	7·78	10·25	12·44	9·03	9·81	14·72	10·43	18·73

for the six groups shown in Table 1 after scores had been adjusted for initial reading age. The main effect did not reach significance (F (5, 137)=1·54).

Reading age is a function both of chronological age and of severity of dyslexia. By transforming reading age scores into T scores one can examine the effect of severity of reading problem independently of age. The correlation between initial reading T score and reading age gain over six months is statistically significant (r (142)=0·242; p<0·01), as is the correlation with total reading age gain over the whole 12 months of study (r (142)=0·439; p<0·01). When the analysis of covariance was repeated using initial T score as covariate when comparing reading age gains of the six groups in Table 1, the main effect again did not reach significance (F (5, 137)=1·68). This confirms that the degree of initial reading impairment can account for differences in outcome between groups. Regardless of age, the more severe a child's initial problem, the less likely he is to make good progress.

The study continued for a further six months, with a partial replication of the first phase. All children who were found to have unstable reference were treated with occlusion, whereas occlusion was discontinued for those with stable reference. Results for this second phase of the study are shown in Table 2.

As all 'unfixed' children were treated at this stage, it is not possible to compare treated and untreated groups, but we can subdivide children in terms of whether stable reference is achieved after occlusion, by comparing two of the initially untreated groups, namely, UNUOF and UNUOU. The amount of reading age gain made in the second phase of the study is not significantly different for these two groups, regardless of whether the T score at the start of the second six months is entered as a covariate (Anova: F (1, 26)=1·3, NS; Ancova: F (1, 25)=2·4 NS). Thus the difference between those who developed fixed reference and those who did not which was observed in the first phase of the study was not replicated in the second phase.

Finally, when the eight groups shown in Table 2 are compared in an analysis of variance on total reading age gain made over 12 months, no significant difference is found (F (7, 136)=1·77: the F ratio is even smaller if the initial reading T score is entered as a covariate).

In conclusion there is no evidence that monocular occlusion in children with unfixed reference results in improved reading scores. When direct comparisons are made between treated and untreated children, differences in amount of reading progress are not statistically significant. There is a significant relationship between development of stable reference and improvement in reading, but this is explicable in terms of differences in initial reading ability. Those children who developed stable reference in the first phase of the study tended to be those whose initial reading problems were less severe.

This work is based on a paper presented at a meeting of the Academia Rodinensis Pro Remediatione at the Royal Society on 16 October 1987. I would like to thank Dr John Stein for inviting me to that meeting in order to put forward a critical view of his work, and for generously providing his raw data for analysis.

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Necrosis of choroidal melanoma: in ciliary artery involvement with temporal arteritis*

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SUMMARY A choroidal melanoma was clinically suspected in one eye of an 84-year-old farmer. At the time of the first examination the patient refused the studies necessary for a certain diagnosis as well as any treatment. Later, when the eye suddenly became blind and painful, it was enucleated. Pathological study revealed necrosis of all ocular contents, but the presence of a choroidal melanoma could still be verified histologically. The ciliary artery supplying the region of the melanoma was involved with giant cell arteritis. General examination of the patient gave support to a diagnosis of temporal arteritis, and steroid treatment resulted in general improvement.

So-called spontaneous necrosis of malignant melanomas of the choroid and ciliary body occurs in about 3·6% of cases and is commonly associated with secondary glaucoma, rubeosis iridis, uveitis, and atrophy of iris and ciliary body.[1] Melanoma necrosis is not a good sign prognostically and may be associated with extraocular tumour extension.[3-5] Fast growing uveal melanomas are predisposed to spontaneous necrosis because of an increased chance of the neoplasms to outgrow their blood supply. Both glaucoma and hypotony may contribute to necrosis of melanomas by causing regional collapse of arteries[5] or stagnation in veins.[6] Necrosis of choroidal melanomas should be expected to occur in temporal arteritis. However, to the best of our knowledge this is the first case with pathological evidence for such an association.

Case report

An 84-year-old farmer was referred by an optometrist for evaluation of suspected glaucoma and was first seen on 21 May 1984. Vision at that time was 20/40 in the right eye and 20/200 in the left. Intraocular pressures measured by applanation were 27 mmHg in the right eye and 15 mmHg in the left. Gonioscopy showed open angles in both eyes. Some glaucomatous cupping with atrophy was found in the right eye. The left fundus, however, contained a golden brown mass under the elevated retina of the inferior temporal periphery. Diagnoses of open angle glaucoma in the right eye and suspected choroidal melanoma in the left eye were made. Medical treatment of the glaucoma was started. The patient was told about the diagnosis of suspected melanoma in the left eye and was advised to obtain a second opinion as a start for the proper management of the tumour. However, he agreed to have the glaucoma treated but refused any further diagnostic or therapeutic steps for the proper identification and treatment of the suspected melanoma.

The patient returned on 31 May 1984. The glaucoma in the right eye was very well controlled. Vision in the left eye had decreased to finger counting at 30 cm. He came back again on 17 July 1984 and stated that he had suddenly become totally blind in the left eye and that the eye had become very painful. Examination showed it to be blind and beefy red, with swollen lids externally. A yellow exudate filled the anterior chamber. The deeper parts could not be seen. Intraocular pressures were 11 mmHg in the right eye and 28 mmHg in the left. The left eye was enucleated on 13 August 1984 and fixed in 10% formalin immediately.

PATHOLOGICAL FINDINGS

The eye was of normal size and did not show areas of direct extrascleral tumour extension. Transillumination did not allow for the demonstration of a clearly

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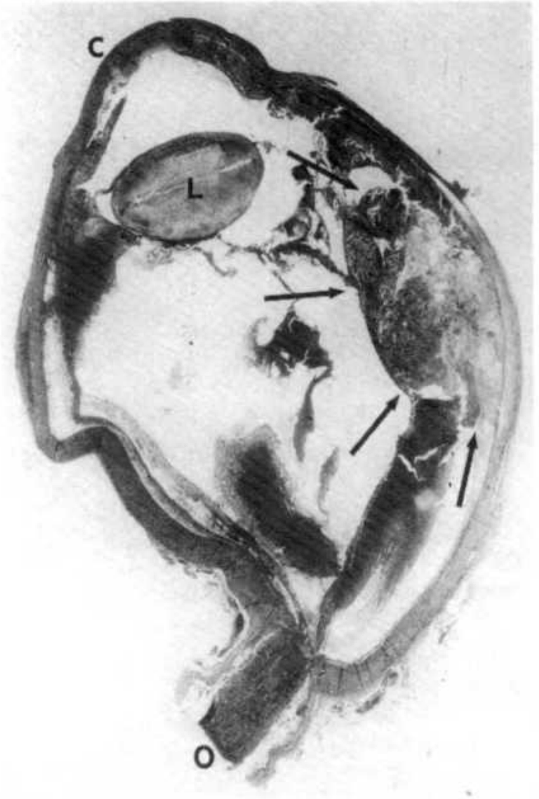

Fig. 1 *Section of the whole eye in horizontal plane with cornea* (C) *and lens* (L) *above, necrotic melanoma (arrows) in temporal choroid, and optic nerve* (O) *below. Paraffin section, H and E stain, ×4.*

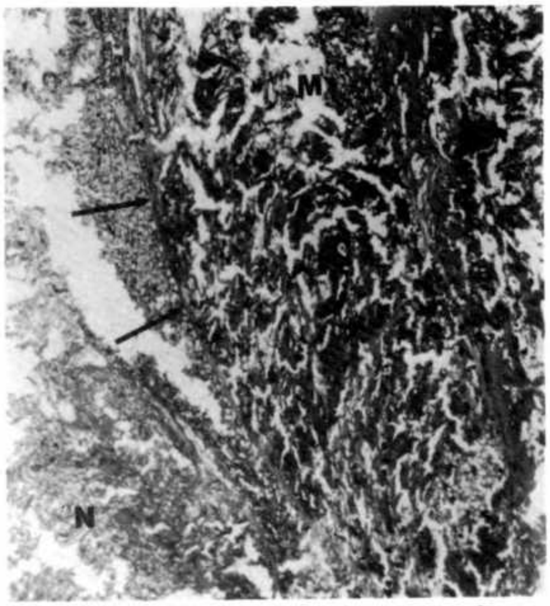

Fig. 2 *Higher power shows necrotic preservation of spindle-shaped cells in area of choroidal melanoma* (M). *Bruch's membrane preserved (arrows). Amorphous necrotic material* (N) *in region of adjacent retina. Paraffin section, H and E stain, ×315.*

outlined shadow in the area of the clinically suspected choroidal tumour. But the whole region of the temporal midperiphery and periphery was optically much more dense than the remainder of the eye—diffusely, without sharp limits. When the eye was opened in a horizontal plane, the anterior chamber was found to be shallow and to contain old blood. The lens was relatively large. A choroidal tumour measuring 9×7×4 mm was found in the temporal midperiphery, in the region of the clinically suspected mass. This was of mushy consistency and black. The retina posterior to the tumour was detached, and the subretinal space contained a mixture of old blood and exudate. Dark blood and debris also filled the vitreous space.

Microscopic sections cut in the horizontal plane (Fig. 1) showed loss of most of the corneal epithelium. The corneal stroma was swollen, and Descemet's membrane was preserved. The corneal endothelium showed diffuse loss of cells but was preserved as a continuous layer. A mixture of blood and exudate containing many pigment-filled macrophages was found in the shallow anterior chamber. The chamber angle was narrow on the nasal side and it was closed by anterior peripheral synechiae temporally. The iris was partly necrotic, but it was preserved in parts of its substance and in its outlines. The ciliary body also showed partial necrosis on the nasal side and total necrosis on its temporal aspects. The lens was swollen and cataractous. It contained small areas of calcification.

The choroid in the midperiphery on the temporal side contained a totally necrotic pigmented tumour (Fig. 1). Higher magnification clearly showed necrotic preservation of bundles of spindle cells of shape and arrangement typical of uveal melanoma (Fig. 2) in the area of the clinically and grossly observed tumour of the choroid. Bruch's membrane was visible on the inner surface of the main mass of the choroidal tumour (Fig. 2). The remainder of the choroid and the retina were also mostly necrotic, but they too were preserved in their outlines and main components. The vitreous space contained blood and exudate in irregular distribution (Fig. 1). Retroretinal haemorrhage was recognised on the temporal side between uveal tumour and optic nerve head. On the nasal side the retina was thickened owing to partial disintegration (Fig. 1). The optic nerve was

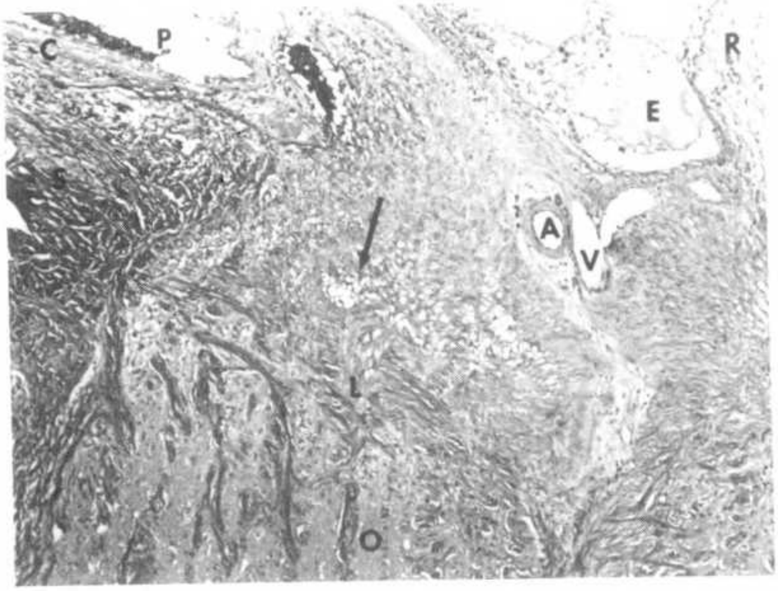

Fig. 3 *Preserved structures of optic nerve head: optic nerve* (O), *lamina cribrosa* (L), *central artery* (A), *vein* (V), *retina* (R), *preretinal exudate* (E), *choroid* (C), *perivascular infiltration* (P), *and sclera* (S). *Arrow points to vacuolic degeneration in nerve substance of disc. Paraffin section, H and E stain,* ×*57.*

preserved in its structures but lacked living cells in its anterior portion. Destruction of nerve substance with formation of lipid vacuoles was seen in the optic nerve head (Fig. 3). The central retinal vessels were open, but they did not contain blood (Fig. 3). The sclera and optic nerve sheaths were normal.

Granulomatous arteritis with epithelioid and giant cells as well as extensive perivascular accumulation of small mononuclear cells was found to involve the long posterior ciliary artery at its entry site on the outside of the sclera on the temporal side (Figs. 4 and 5). Giant cells of the Langhans type were located on the outside of the arterial muscle layer next to degenerating inner elastic lamina (Fig. 5) and there also were local degeneration of arterial muscle cells and some intimal fibrosis (Fig. 5). Serial sections showed that the same artery on its course into the sclera and choroid towards the necrotic choroidal tumour did not exhibit signs of arteritis. While the artery contained blood in its lumen in the zone of inflammatory involvement on the outside of the sclera (Fig. 5), it was filled with exudate only—and not with blood on its further course in sclera and choroid into the inner eye.

A pathological diagnosis of temporal arteritis in an eye with a necrotic choroidal melanoma was made. Clinical examination showed a sedimentation rate of 27 mm/h associated with other signs and symptoms of possible temporal arteritis. Treatment with prednisone 10 mg four times daily was started. Vision in the right eye remained good. The patient is still alive and without evidence of metastatic or recurrent melanoma.

Discussion

Cranial arteritis is a granulomatous arteritis and generally occurs in old people. Typical findings are a much raised blood sedimentation rate as well as fever and other signs of generalised disease.[7-10] But in its so-called occult form it may present with sudden loss of vision.[11] The visual loss is usually irreversible, but at

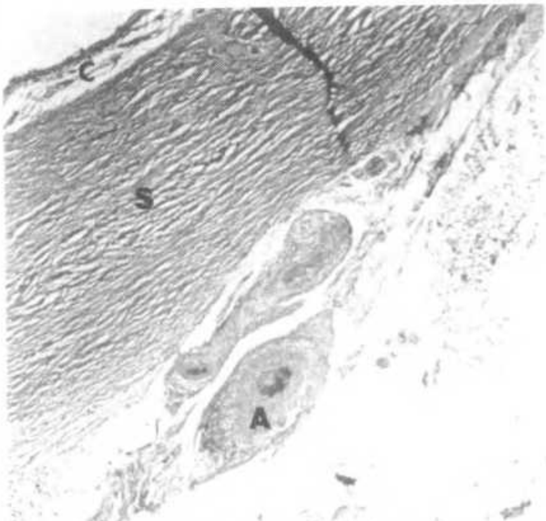

Fig. 4 *Posterior temporal aspect of sclera* (S) *and choroid* (C) *with long posterior ciliary artery* (A) *exhibiting granulomatous arteritis directly before entry into sclera* (S). *Paraffin section, H and E stain,* ×*54.*

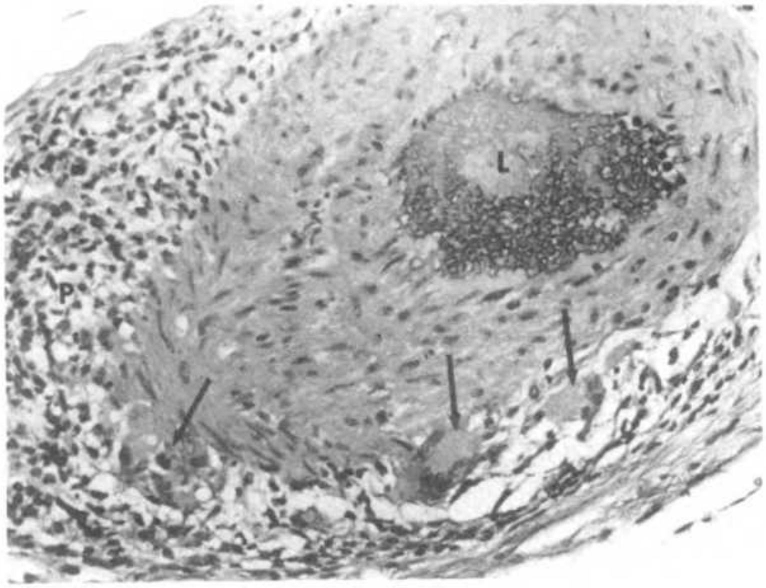

Fig. 5 *Long posterior ciliary artery on outside of sclera with massive perivascular infiltration* (P) *and giant cells (arrows) next to degenerating inner elastic lamina in its wall. Arterial lumen* (L) *preserved and filled with blood. Paraffin section. H and E stain. ×330.*

first it usually involves only one eye. Histological examination of eyes blinded by temporal arteritis usually reveals granulomatous inflammation in extrascleral portions of the ciliary arteries or extradural parts of the central retinal artery. Special stains show the granulomatous reaction to be centred on degenerating elastic fibres and smooth muscle.[11 12] Rubeosis leading to secondary glaucoma further complicates the clinical picture of temporal arteritis.[13-15] But there was no evidence of any relationship between the glaucoma in the right eye and the temporal arteritis in the present case.

Temporal arteritis is a disease of many faces, and with the advances in diagnosis and therapy it is rarely seen now in its fully developed form. It should be suspected in cases of sudden visual loss in old patients, and a temporal artery biopsy is considered the clinically most reliable method for its recognition. The histological observation of typical giant cell arteritis in the long posterior ciliary artery supplying the uveal region of the melanoma in the present case counts at least as the equivalent of a positive temporal artery biopsy diagnostically. The giant cell arteritis in this ciliary artery, furthermore, may explain the necrosis of the melanoma. Massive necrosis of parts of the inner eye is known to produce necrotoxins and to have a tendency to involve all intraocular structures. In this process an endophthalmitis-like syndrome with much pain is apt to develop.

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Computerised intraocular lens calculation: clinical results and predictability

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SUMMARY The predictability of a theoretical, computer-assisted IOL calculation method and of the Sanders-Retzlaff-Kraff (SRK) method was evaluated from pre- and postoperative biometry in 110 cataractous patients subjected to a routine IOL calculation. With the theoretical method and the preoperative data the refraction was on the average 0·72 D (SD 0·78) more myopic than expected, an error which could be corrected for by (1) substituting the assumed postoperative chamber depth by the actual mean value and (2) adding 0·16 mm to the preoperative axial length. With the postoperative data the error was 0·05 D (SD 0·78) ($p>0·05$). By the SRK method the refraction was 0·15 D (SD 0·71) and 0·37 D (SD 0·69) more hyperopic than expected with the pre- and the postoperative data respectively. These offset errors could be corrected for in either case by adjusting the assumed A constant in the SRK formula. With appropriate empirical corrections for offset errors the theoretical and the SRK method were similar in accuracy, that is, about 82% of the predictions within ±1 D, 99% within ±2 D, and 100% within ±3 D error. The variation in postoperative refraction after computerised IOL calculation was about one-third of the variation previously seen after implantation of standard power IOL.

The calculation of intraocular lens (IOL) power has been possible since the introduction of accurate ultrasonic equipment for the measurement of the axial length of the eye. The first formulae were theoretical and derived from laws of paraxial imagery by means of various sets of assumptions.[1-3] The more recent empirical formulae represent a different approach based on a statistical regression analysis of the actual refraction observed in a large number of operated patients.[4-7] There seems to be no general agreement on which approach is the more accurate,[8-10] and opinions still differ on the importance of doing a routine IOL calculation.[11-14]

We have recently developed a computer assisted theoretical approach to IOL calculation using assumption free formulae within the theory of Gaussian optics. This method represents an improvement over current theoretical methods in the calculation of corneal power and in dealing with the principal planes.[15] In a previous study this method was found to be more accurate than the Sanders-Retzlaff-Kraff (SRK) formula in the prediction of ametropia.[16]

In this investigation we report the results after routine IOL calculation aiming for about −1 D postoperatively. In addition, the prediction accuracy of the theoretical and the SRK method is evaluated on both the pre- and the postoperative data.

Material and methods

One hundred and ten patients, 43 males and 67 females, in the age range 57–94 years, mean 75·4 (SD 8·0) years, were studied. They constituted a consecutive series of patients undergoing routine cataract extraction on an outpatient basis from February to June 1986. During the study it was a routine procedure to do an intracapsular cataract extraction with the implantation of an anterior chamber lens (Intermedics 44B, a planoconvex flexible loop lens) in patients with no contraindications against IOL implantation, with no history of retinal detachment, with no previous cystoid maculopathy, and with no excessive myopia (more

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than 6 dioptres axial myopia). The operative procedure was cryoextraction after corneal incision and zonulysis.

Before surgery the axial length and the anterior chamber depth were measured with ultrasonic A-scan (O cuscan, Sonometrics) using a 10 MHz solid transducer probe and an electronic reading system. The velocity of ultrasound was assumed to be 1550 m/s for the whole phakic eye and 1532 m/s for the anterior chamber (from corneal surface to lens surface).[17] The corneal curvature was measured in two meridians with either a manual (Zeiss) keratometer (one-third of the cases) or with an automatic keratometer (Nidek KM-800) (two-thirds of the cases) Both keratometers were calibrated and found to give identical results.

The theoretical prediction of IOL power, the biological lens power, and the ocular magnification were calculated by a theoretical computer assisted method as previously described.[15] Preoperatively, the postoperative chamber depth was assumed to be 3·0 mm in all cases. The IOL power was selected aiming for about −1 D postoperatively with tolerable aniseikonia. A maximum aniseikonia of 10% was accepted, depending on the vision of the fellow eye. For the present study the computer program was integrated with a database and written in a compiled version of BASIC (TURBO BASIC by Borland International) and run on an IBM AT personal computer.

The SRK[7] prediction of postoperative refraction was calculated as:

$$R=(P-I)/1{\cdot}5,$$

where R is refraction, I is power of implant, and P is emmetropia yielding power of IOL, calculated as:

$$P=A-2{\cdot}5\,Ax-0{\cdot}9\,Fc,$$

where Ax is axial length and Fc is corneal power calculated on the assumption of a corneal refractive index of 1·3375. The A constant was assumed to be 114·8, as stated by the manufacturer.

Six months after surgery the refraction was recorded as the correction giving the best Snellen visual acuity at 6 m. All refractions were calculated as spherical equivalents. To be accepted for the study a final visual acuity of 20/40 or better was required. Again, the corneal curvature, the anterior chamber depth, and the axial length were measured. The axial length was corrected for the presence of the IOL by assuming a velocity of ultrasound in polymethyl methacrylate (PMMA) of 2981 m/s.[18] With the present average IOL thickness of 0·9 mm this was the equivalent of adding 0·4 mm to the reading obtained with the velocity set at 1532 m/s.

STATISTICAL ANALYSIS

The statistical analysis was by distributional methods, and the results were generally stated as arithmetical means±one standard deviation (SD). For comparison of paired data Student's paired *t* test was applied.[19]

Table 1 *Pre- and postoperative data of 110 patients with computerised calculation of IOL power; means with SD in parentheses*

	Refraction (D)	*Corneal power (D)*	*Lens power (D)*	*Axial length (mm)*
Pre-	0 16	42·99	23 08	23 16
op	(2 50)	(1 51)	(3 26)	(1 02)
Post-	−1 59	42 98	20 11	23 31
op.	(0 75)	(1·53)	(2 52)	(1 04)

Results

The pre- and the postoperative clinical data appear in Table 1. The mean refraction after surgery (SD) was −1·59 D (0·75), range −3·1 to +1·1 D. This was produced by the implantation of IOL powers ranging from 12·5 to 28 D (mean 20·11 D). The mean difference between the biological and the implant lens power was −2·0 D (3·46). The mean corneal power (spherical equivalent) did not change significantly after the operation, the mean change being −0·01 D (0·38). The axial length, however, was found to increase by 0·15 mm (0·24) ($p<0{\cdot}001$).

The increase in ocular magnification (aniseikonia) with correction was on the average 2% (SD 4·2), with a range of −7 to 19%. The patients in whom an increase of more than 10% was allowed were myopes with a fellow eye of poor vision to preclude binocularity.

The error of prediction with the theoretical and the SRK method using pre- and postoperative sets of data have been summarised in Table 2. For the

Table 2 *The refractive prediction error in 110 patients with computerised IOL calculation Method A=theoretical method with uncorrected preoperative data Method B=theoretical method and preoperative data, substituting the assumed postoperative chamber depth by the actual value of 2 82 mm. Method C= theoretical method with postoperative data; Method D=SRK method with preoperative data Method E=SRK method with postoperative data Means with SD in parentheses*

Method	*Error (D)*	*Range (D)*
A	−0 72* (0 78)	−2·70 (2 26)
B	−0 45* (0 76)	−2 33 (2 36)
C	+0 05‡ (0 78)	−1 92 (1 75)
D	+0 15† (0 71)	−1 73 (2 45)
E	+0 37* (0 69)	−1 33 (2 42)

*Different from zero ($p<0\ 001$) †Different from zero ($p<0\ 05$)
‡Not significant ($p>0\ 05$)

theoretical method the error was −0·72 D (0·78) when the preoperative data were used in the calculations This mean error was significantly different from zero (p<0·01). Some of this error was due to an overestimation of the postoperative chamber depth, the actual value of which was found to be 2·82 mm (0·29). When this value, rather than the presumed value of 3·00 mm was used in all calculations, the mean prediction error reduced to −0·45 D (0·75). The residual error of 0·45 D more myopic than expected could be corrected for by adding 0·16 mm to the preoperative axial length. When the postoperative data were used in the calculations, the error was −0·05 D (0·78), which was not significantly different from zero (p>0·05).

For the SRK method the preoperative error of prediction was +0·15 D (0·71). This error was significantly different from zero (p<0·05), and could be corrected for by adding 0·22 D to the A constant or, alternatively, by subtracting 0·09 mm from the axial length. With the postoperative data the error was +0·37 D (0·71) (p<0·01) The mean error could be corrected for by adding 0·55 D to the A constant or by subtracting 0·22 mm from the axial length.

With the appropriate empirical corrections for observed offset errors, the predictability of the theoretical method was comparable in accuracy with that of the SRK method, as shown in Fig. 1. The observed variation around the mean value was not significantly different between the two methods (p>0·05 by F test). With either method about 82% of the predictions were within ±1 D, 99% within ±2 D, and all within ±3 D error.

Discussion

Patients are generally satisfied with a postoperative refraction in the slightly myopic range. Without spectacles the patients enjoy comfortable distant vision, and many are able to read provided the astigmatism is not too large. The present study has shown that it is possible to aim for this refractive range by a routine calculation of IOL power. In Fig. 2 the present results have been compared with the variation observed after implantation of a standard power lens (data from previous study[20]). The narrowing of the postoperative range after computerised IOL calculation represents a reduction to one-third of the variation seen after standard power lens (95% confidence interval of 3 D versus 8·5 D after standard power lens). Large refractive errors are hereby virtually avoided, and the beneficial effect of a routine IOL calculation is clearly demonstrated.

The sources of error in IOL calculation are manifold. Measurement errors will always be responsible for a random variation whichever method is used. By

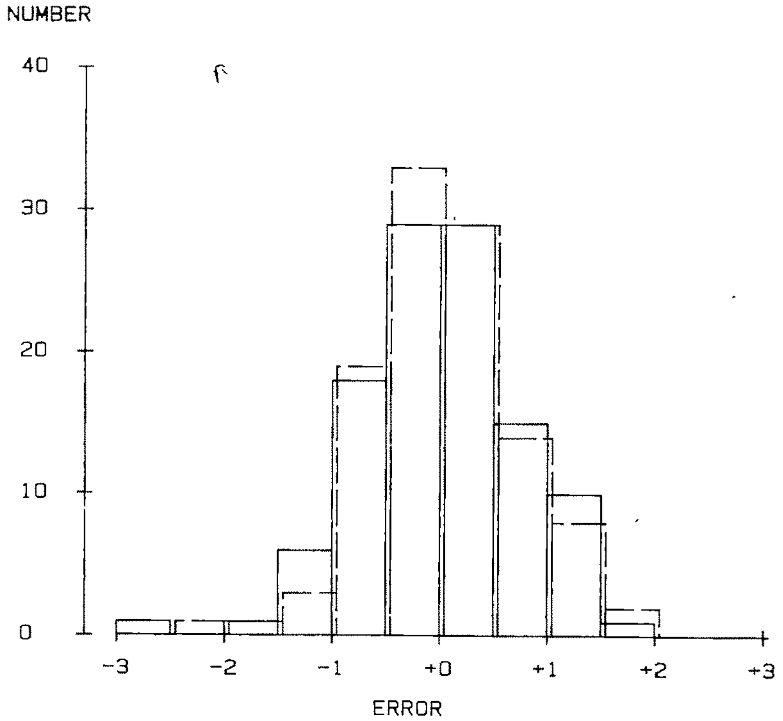

Fig. 1 *Error (in dioptres) of prediction of postoperative refraction in 110 patients with computerised IOL calculation The predictions have been corrected for offset errors by adjusting the postoperative chamber depth and the axial length for the theoretical method, and by adjusting the A constant for the SRK method Solid columns=theoretical method, interrupted columns=SRK method.*

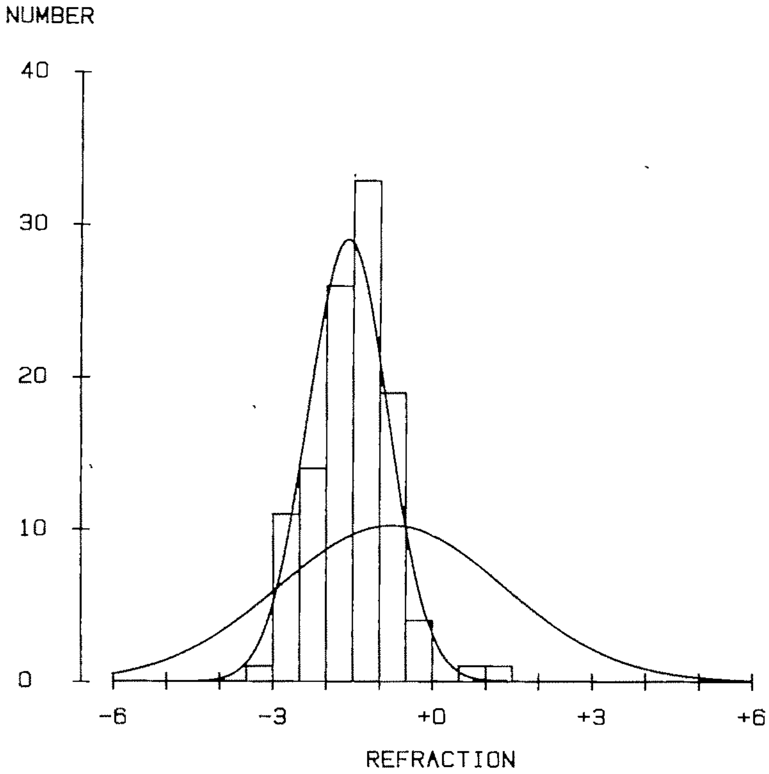

Fig 2 *The distribution of the postoperative refraction after routine IOL calculation The histogram was not significantly different from a normal distribution by χ^2 test ($p>0{\cdot}05$) For comparison, the results after implantation of standard power IOL have been included (broader distribution)*

analysing the systematic errors, however, it is possible to correct for offset errors which may show up in the theoretical as well as in the empirical method. For the theoretical method the accuracy can be improved by adjusting the postoperative chamber depth according to the value actually observed.[8] No attempt was made in the present study to make an individual prediction of the postoperative chamber depth, though such methods have been described for another type of anterior chamber lens.[21] It is possible that an improved prediction of the individual IOL position may further increase the accuracy of the theoretical method.

When the correction for actual mean postoperative chamber depth has been done, a residual error may remain, which may have different sources. An 'inborn error' of the theoretical approach is the small distance from the vitreoretinal surface to the sensory elements of the retina, which apparently calls for the addition of a small distance to the distance as measured by ultrasound. Many other errors exist, however, such as errors in calibration, the method of alignment, possible compression of the globe during measurement, density of the cataract, difference between keratometry and true corneal power, and optical aberrations of the eye, etc., all of which may make the distance measured by ultrasound differ from the axial length in the optical sense. It is difficult to make a-priori recommendations as to the magnitude of these errors and their possible correction. In the present study the residual error was the equivalent of 0·16 mm added to the preoperative axial length. For other systems, especially for other types of equipment for axial length measurements, it is possible that other corrections may be necessary.[22 23] This is how to 'personalise' the IOL calculation according to the theoretical approach.

When the postoperative data were used in the 'predictions', it was not necessary to use any axial length correction with the theoretical method. In view of the retinal thickness problem this may seem surprising, but because of the complexity of possible errors, as stated above, it is not certain that all corrections should be in the form of *addition* to the axial length. Along with the disappearance of the axial length correction an increase in the axial length was noted Rather than representing a true enlargement of the globe after surgery, this apparent increase may indicate a higher velocity of ultrasound in the cataractous lens than previously assumed This is in accordance with the findings in aphakic subjects.[24]

The SRK approach may be adapted to the individual patient by adjusting the A constant in the regression formula. In this way any offset error may be corrected, but the variation round the mean remains unchanged. This is the equivalent of adjusting the average postoperative chamber depth and the axial length in the theoretical method. It is often stated that personalising the A constant accounts for differences in surgical technique and style of IOL. However, corrections are made for many other errors, such as calibration errors and differences in measuring technique. Because the axial length determination is probably the most vulnerable step in the IOL calculation, an alternative adjustment of the SRK approach is to correct the axial length by the amount of the empirically observed offset error. This would give as accurate results.

The present study has shown that there is no significant difference between the accuracy of the SRK and the theoretical approach when aiming for the near emmetropia region in normal cataractous patients. This result is in contrast to the results in ametropia, for which the theoretical method has been shown to be more accurate.[16] It is not surprising that the SRK method works at its best for the refractive range for which it was derived. To improve the accuracy of the empirical method in the extreme range new classes of non-linear regression formulae have been described, which may work better for unusually long and short eyes.[25,26]

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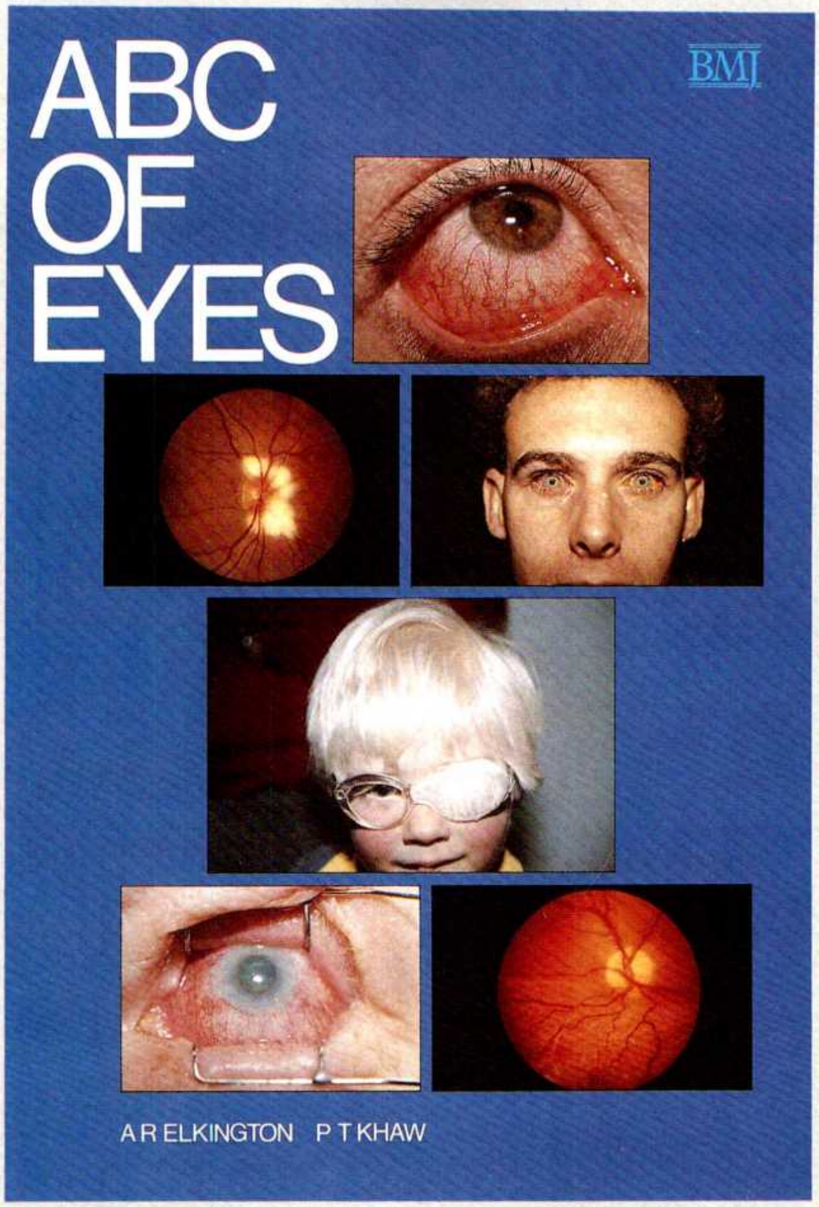

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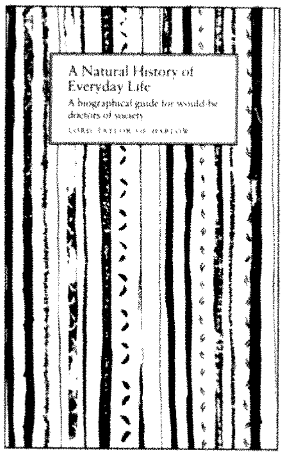
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Screening for uveitis in juvenile chronic arthritis

JACK J KANSKI

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SUMMARY Three hundred and fifteen patients with anterior uveitis associated with juvenile chronic arthritis (JCA) were studied in order to identify the various risk factors for uveitis. Girls were more susceptible to uveitis than boys by a ratio of 3:1. In 94% of cases the uveitis was diagnosed after the development of arthritis. The risk of uveitis was small after seven or more years had elapsed from the onset of arthritis. Patients with pauciarticular onset JCA had the highest risk of uveitis and systemic onset patients the least risk. The presence of circulating antinuclear antibody was also an important marker for an increased risk of uveitis. A regimen for routine screening of patients is suggested.

Juvenile chronic arthritis (JCA) is a rare idiopathic inflammatory arthritis occurring before the sixteenth birthday. The condition was formerly referred to as Still's disease, and in the United States it is frequently called juvenile 'rheumatoid' arthritis. About 20% of patients with JCA develop anterior uveitis, which is frequently bilateral.[1-4] The intraocular inflammation is typically asymptomatic, and, unless it is detected and treated at a relatively early stage, some patients are at risk of developing severe visual impairment.[5] It is therefore important to identify and screen patients who are at increased risk of ocular complications. Similarly, those with little or no risk should also be identified in order to spare the patients and parents the inconvenience of unnecessary and time wasting visits to the ophthalmologists.

The main purpose of this study is to describe the clinical and immunological characteristics of a large number of patients with JCA in relation to the likely risk of uveitis and to give guidelines to the necessity for routine screening.

Patients and methods

This study comprises 315 patients with anterior uveitis who fulfilled the criteria for the diagnosis of JCA. Special investigations included *x*-rays, synovial biopsy when indicated, and tests for IgM rheumatoid factor. Tests for circulating antinuclear antibodies (ANA) were performed on 277 patients. The author personally examined most of the patients over a 10-year period (January 1975 to December 1984). In most cases the diagnosis of uveitis was made when the patient attended a combined eye-joint clinic. The following information was obtained from the medical records: sex, age at onset of arthritis, age at time of diagnosis of uveitis, extent of arthritis during the first three months, subsequent course of joint involvement, presence of extraarticular systemic features, and presence of IgM rheumatoid factor and ANA.

Results

Of the 315 patients 234 (74%) were girls. The mean age of the patients at the onset of JCA was 3 years and 8 months (range 6 months to 16 years); 62% of children were under the age of 4 years when they developed arthritis and 90% were under the age of 8 years.

INTERVAL BETWEEN ONSET OF JCA AND DIAGNOSIS OF UVEITIS

In 295 patients (94%) JCA preceded the diagnosis of uveitis. Of these patients 158 (53%) developed uveitis within two years of the onset of JCA, and in 267 (90%) the interval was not longer than seven years. There were, however, three patients in whom the interval between the onset of JCA and the diagnosis of uveitis was over 20 years. In two of these the uveitis was first diagnosed on a routine slit-lamp examination when the patients were in their mid 20s, and in another the diagnosis was made at the age of 36 years when an optician noticed bilateral lens

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opacities at a routine refraction. In 20 patients (6%) the diagnosis of uveitis antedated the development of JCA. Of these patients 17 developed JCA within four years, and in one patient joint involvement was delayed for nine years. When last examined 14 patients in whom uveitis antedated arthritis were aphakic in at least one eye, and of 29 eyes in 16 of these patients that had an adequate period of follow-up nearly half (14) had a visual acuity of counting fingers or less.

ARTICULAR FEATURES

The 315 patients were divided into three groups according to the mode of onset of JCA and the extent of joint involvement during the first three months. Table 1 shows the number of patients in each group and Table 2 shows the sex distribution in each group.

Group 1—pauciarticular onset JCA. In 284 patients, of whom 75% were girls, the arthritis presented with and remained confined to fewer than five joints during the first three months of the disease. The most frequently involved joints were the knees, followed by the ankles and elbows. However, in one patient the disease presented with involvement of only one joint of the ring finger and in another with arthritis of a single toe.

According to the subsequent course of joint involvement the patients in this group were divided into the following three subgroups. (*a*) Persistently monoarticular JCA. In 29 patients the arthritis remained confined to one joint (invariably the knee). In some patients changes secondary to arthritis caused the affected leg to be slightly longer than the normal leg. In other patients the arthritis resolved without residua. Two patients in this subgroup developed uveitis prior to the onset of JCA. (*b*) Persistently pauciarticular JCA. In 133 patients between two and four joints became invovled subsequently. (*c*) Extended pauciarticular JCA. In 122 patients the arthritis subsequently spread to five more joints (that is, became polyarticular). In some patients severe joint deformities required surgical correction, and six patients developed secondary amyloidosis. In this subgroup six patients had uveitis prior to the onset of JCA.

Group 2—polyarticular onset of JCA. In 27 patients, of whom 70% were girls, the arthritis involved five or more joints during the first three months of the disease. The most frequently affected joints were the knees followed by the wrists and ankles.

Group 3—systemic onset JCA. In four patients (one girl) the disease was heralded by a high remittant fever which was characteristically at its height at night and normal next morning. In order to fulfil the criteria for systemic onset JCA at least one of the following signs was also present: a maculopapular (Still's) rash, generalised lymphadenopathy, splenomagaly, hepatomegaly, and pericarditis. All four patients in this group subsequently developed polyarthritis. It is important to emphasise that nearly half (153 of 315) the patients with JCA had a polyarthritis some time during the course of their disease.

SYSTEMIC FEATURES

Extrarticular systemic features, which are summarised in Table 3, were present at some time during the course of the illness in 35 out of 311 (11%) patients in groups 1 and 2. Several patients had more than one feature. Three patients died from complications of JCA. One died during sleep as a result of dislocation of his atlanto-occipital joint, another died from renal failure as a result of secondary amyloidosis, and the third was completely incapacitated and bedridden as a result of extremely severe polyarthritis and died of heart failure.

IMMUNOLOGICAL FEATURES

All patients gave negative results for IgM rheumatoid factor but 208 out of 277 (75%) were ANA positive. Table 4 shows that there was no difference between patients with pauciarticular and polyarticular onset JCA, though three patients with systemic onset JCA were all negative. There appeared to be no correla-

Table 1 *JCA subgroups*

JCA onset	*Number*	*Percentage*
Group 1 (pauciarticular)	284	90
Group 2 (polyarticular)	27	9
Group 3 (systemic)	4	1

Table 2 *Sex distribution in JCA subgroups*

JCA onset	*Girls*		*Boys*		*Total*
	Number	*Percentage*	*Number*	*Percentage*	
Group 1 (pauciarticular)	214	75	70	25	284
Group 2 (polyarticular)	19	70	8	30	27
Group 3 (systemic)	1	25	3	75	4

Table 3 *Systemic features*

Feature	*Number*		*Total (311)*
	Group 1 (284)	*Group 2 (27)*	
Cutaneous			
Still's rash	1	1	2
Morphea	1	1	2
Erythema nodosum	1	–	1
Psoriasis	8	3	11
Reticuloendothelial			
Hepatomegaly	2	–	2
Splenomegaly	6	1	7
Lymphadenopathy	3	1	4
Gastrointestinal			
Regional ileitis	1	–	1
Ulcerative colitis	1	1	2
Cardiovascular			
Pericarditis	1	–	1
Aortic incompetence	1	1	2
Secondary amyloidosis	6	–	6
Remittent fever	–	1	1
Enlarged salivary glands	1	–	1

tion between the level of ANA titre and the activity of either eye or joint inflammation.

Discussion

Although, in general, JCA is more common in girls than in boys by a ratio of 3:2,[10-12] it appears that girls carry a distinctly higher risk of ocular complications. In this study 74% (234 of 315) were girls, and the incidence in other studies ranges between 60% and 92%.[1 2 4 7 13-18] It is also evident that girls are more susceptible to chronic anterior uveitis than boys, irrespective of whether or not they have JCA.[19] At present no adequate explanation can be given for the increased susceptibility of girls to uveitis.

In 90% of cases the interval between the onset of JCA and the diagnosis of uveitis was less than seven years. It therefore appears that the risk of uveitis is small after seven or more years have elapsed from the time of onset of arthritis, so that the intervals between routine screening can be extended, but it is impossible to say with certainty when the risk of uveitis is nil. It is therefore recommended that an annual screening should still be performed even when the patients with JCA reach adulthood. Although only 20 (6%) of the patients were found to have uveitis prior to the onset of JCA, there is little doubt that the type of chronic indocyclitis that is typically associated with JCA can occur in the absence of joint involvement, particularly in girls, and in fact the majority of children with chronic iridocyclitis do not develop arthritis.[18 19] Nevertheless, it should be stressed that, although 17 out of 20 patients in this study developed JCA within four years of the diagnosis of uveitis, in one patient joint involvement was delayed for nine years. It would therefore seem reasonable to exclude the possibility of subsequent JCA only after a prolonged period of follow-up.

Table 4 *ANA in subgroups of JCA (277 patients)*

JCA onset	*ANA positive*	
	Number	*Percentage*
Group 1 (pauciarticular)	189/248	76
Group 2 (polyarticular)	19/26	73
Group 3 (systemic)	0/3	3

Although there was no correlation between the activity of joint and eye inflammation, a striking association was apparent between the mode of onset of JCA and the subsequent risk of uveitis. Although about 30% of patients with JCA have a systemic onset,[12] in this study only four out of 315 patients had this mode of presentation. It is therefore apparent that uveitis is sufficiently rare in this group of patients for an annual screening to suffice.

About 20% of all JCA patients have a polyarticular onset,[12] and in this study 9% had this mode of presentation. It is difficult to compare these findings with those of other reports, because none enumerate the number of joints involved during the first three months of the disease but merely indicate the extent of arthritis when the patient was last examined. Because the risk of uveitis in the group with polyarticular onset JCA is higher than in the systemic onset group, a six-monthly slit-lamp examination would seem appropriate.

The most frequent mode of presentation of JCA, accounting for about 50% of cases, is monopauciarticular.[12] In some patients the disease remains monopauciarticular, while others subsequently develop polyarthritis. It is this group with monopauciarticular onset of JCA that is of particular importance to ophthalmologists because of the high risk of ocular complications. In this study 90% of patients had this mode of presentation. However, it should be emphasised that 43% subsequently developed polyarticular disease, which was complicated in six patients by secondary amyloidosis. From these findings it is recommended that, when assessing the risk factors of uveitis, the ophthalmologist should take a careful history of the mode of onset of arthritis and ignore the extent of joint involvement when he first examines the patient. This is because nearly half of all patients with JCA will have a polyarthritis sometime during the course of their disease.

Table 5 *Screening regimen for uveitis in JCA*

Risk factor	*Frequency of screening*
Systemic onset	Annual
Polyarticular onset	6-monthly
Pauciarticular onset	3-monthly
Positive ANA	2-monthly

Conversely, in some patients the arthritis may be mild, transient, and confined to only one joint. These patients may present with uveitis and the past history of arthritis may be overlooked by the ophthalmologist or forgotten by the patient or parents. Because of the high risk of uveitis in patients with pauciarticular onset JCA, a three-monthly screening is recommended for at least seven years from the onset of JCA.

It is interesting to note that, although only four patients with uveitis had the typical systemic onset of JCA, there were several patients in groups 1 and 2 who had various combinations of systemic features but who did not fulfil the criteria for true systemic onset JCA. It therefore appears that the presence of systemic features does not necessarily indicate a low risk of uveitis as in the true systemic onset group.

The finding that all patients with JCA were negative for rheumatoid factor confirms the fact that seropositive children with 'juvenile rheumatoid arthritis' resemble their adult counterparts and do not carry an increased risk of uveitis. Routine screening of asymptomatic patients in this group of patients is therefore unnecessary. However, the high incidence of positive findings for ANA in this study of 75% and an incidence of 71%[illegible] reported in other studies, as opposed to an incidence of 30% in JCA patients without uveitis,[illegible] serve to emphasise the need for frequent routine screening of all ANA positive patients. It is suggested that this group should be screened at two- to three-month intervals for at least seven years from the time of onset of JCA, particularly if they also have disease of pauciarticular onset. The recommended regimen for screening during the first seven years is summarised in Table 5.

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Alterations of the anterior lens capsule associated with climatic keratopathy

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SUMMARY We describe changes in the anterior lens capsules of older people in Somalia, a country which is close to the equator and with large areas of sand, often highly reflective of sunlight. The capsule changes are confined to the central pupillary area. In order of apparently increasing severity they consist of a white opalescence ('frosting'), an elevation in front of the contour of the rest of the lens to form a plateau, and a 'bag' or herniation of the lens capsule through the pupil. Plateau and bagging taken together are strongly associated with climatic keratopathy (and by inference with reflected ultraviolet exposure), weakly associated with exfoliation syndrome, inversely related to the degree of cataract, and interfere severely with vision.

Deformations of the anterior lens capsule have been noted among approximately 10% of patients aged over 50 in a new eye unit in Afgooye, Somalia, and less frequently among females. These range from a plateau shaped elevation in the pupillary area through an anterior lenticonus to a frank herniation or 'bagging' of the lens capsule through the pupil. At the same time it has been frequently observed that the anterior lens capsule is thinner than normal and much more friable at lens extraction than would be considered normal in other parts of Africa or in Europe.

Severe climatic droplet keratopathy (synonyms: spheroidal degeneration of the cornea, actinic keratopathy, solar keratopathy, Labrador keratopathy) and exfoliation syndrome (pseudoexfoliation of the lens) were both frequent in this population. The questions we asked were whether the anterior lens capsule deformation could be firmly related to climatic keratopathy and by inference to ultraviolet light (UV) exposure, to exfoliation, or to the presence or absence of cataract.

Subjects and methods

The study was conducted at Centre Afgooye, a small eye unit 30 km from the capital city, Mogadishu. This is a joint project of the Government of Somalia and the Christoffel Blindenmission, in partnership with the International Centre for Eye Health. The patients came not only from the surrounding area but from all over the country and occasionally from contiguous countries. The investigation was planned as a case control study. Possible cases, suspected of showing the anterior lens capsule distortion, were selected by torch and loupe examination by the screening doctors and nurses for more detailed study. Controls were obtained by examining in detail every second patient aged over 50 until sufficient numbers were obtained without lens capsule changes. The patients admitted for surgery on three successive weeks were also examined and classified as cases or controls.

For each case and control the hospital number, age, sex, and, when possible through interpreters, the area of usual residence and occupation were recorded on a separate form. Visual acuity was recorded by medical assistants using an E chart. The anterior segment was examined with a Takagi slit-lamp (similar to the Haag-Streit 900). A drawing of the cornea was made. Climatic keratopathy was graded according to previous definitions[1] (summarised in Table 1). The intraocular tensions were measured either by Schiøtz tonometry or the Mark II Perkins hand-held applanation tonometer (Clement Clarke Ltd), or occasionally confirmed as normal by palpation if there was no time for formal pressure measurement.

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Table 1 *Definitions of categories of climatic keratopathy (spheroidal degeneration of the cornea)*

Grade 0: No keratopathy, or eyes with traces of keratopathy—that is, few 'droplets' in one or other margin but not symmetrically on both sides of the cornea
Grade 1: The fine, translucent grey colour or colourless deposits are confined to both nasal and temporal marginal strips of the cornea
Grade 2: The deposits extend into the optic axis but are not sufficiently dense to measurably reduce vision
Grade 3: The grey deposits extend across the pupillary area in a band which reduces vision
Grade 4: In addition there are raised yellow or brown nodules, elevating the epithelium, which, however, is intact—unless the excrescences are in the process of flaking off

The pupils of each person included in the study were dilated with one drop of phenylephrine hydrochloride 5%. If dilatation was inadequate this was repeated, and occasionally cyclopentolate hydrochloride 1% added. The lens of each eye was then re-examined with the slit-lamp and direct ophthalmoscope with particular attention to three features: contour of anterior lens capsule, presence of exfoliation syndrome, and presence and stage of cataract.

The configuration of the centre of the anterior lens capsule was classified into one of four categories, as outlined in Table 2. The eye was disqualified if there was a mature cataract so that the anterior lens capsule was wrinkled or stretched without unequivocal forward protrusion in the pupillary area.

Careful inspection of the capsule of controls often revealed a slightly whiter area of the grey capsule in the area exposed by the undilated pupil, which we called 'frosting' (Fig. 1). This was remarkably frequent in eyes without any other apparent intraocular pathology. Therefore, for a diagnosis of exfoliation to be made, it was necessary to see in addition either white/grey flakes resembling dandruff on the pupil border or the characteristic light grey membrane of exfoliation material on the periphery of the lens capsule, often with curled anterior edges.

Table 2 *Definitions of categories of lens capsule change*

The configuration of the anterior lens capsule in the pupillary area was allocated to one of four categories

1 Normal: Normal curvature, normal shagreen and no 'frosting' of surface
2 Frosting: This was a central zone of capsule representing the area defined by the constricted pupil, which had a whitish opalescence (Fig. 1). It resembled the appearance of the same area in the exfoliation syndrome, but without the associated features of exfoliation. The curvature of the anterior lens capsule was smooth and continuous
3 Plateau: In addition to 'frosting' the pupillary area of capsule was elevated above the surrounding lens when viewed in the slit beam and protruded forward, but the central area remained flat (Fig. 2)
4 Bagging: The capsule and lens contour protruded forwards within the confines of the undilated pupil. The contour was often conical, and could be described as an anterior lenticonus. In other cases the 'bag' was irregular in shape and cross section and was sometimes a frank 'herniation' of lens capsule and contents through the pupil (Figs. 3–6).

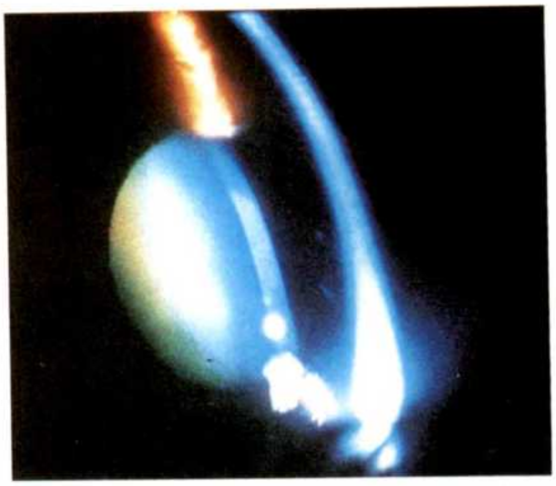

Fig. 1 *The whitish appearance of the central anterior lens capsule described as 'frosting', in the presence of early grade 3 climatic keratopathy. The curve of the anterior lens capsule remains smooth and continuous.*

When severe grade 3 or grade 4 climatic keratopathy was present and it was not possible to see clearly the centre of the lens capsule with the eye looking straight ahead, the patient's gaze was directed downwards. It was then possible to examine the upper half of the pupillary area of capsule with the slit-lamp, looking through clear cornea over the band of keratopathy; similarly the lower part of the pupillary area was seen with the eyes turned upwards. With the mirror of a gonioscopic lens in the 12 or 6 o'clock positions additional detail of the contour of the central capsule could be studied and signs of exfoliation confirmed. We are thus confident that the observed capsule changes are not an optical illusion caused by a distorted view through a band of keratopathy.

Cataract, if present, was classified into one of three stages, summarised in Table 3, against the red glow of the fundus. The appearance of the fundus was also recorded if it could be seen with the direct ophthalmoscope.

The diagnoses and visual acuities of all the new patients seen in this clinic are being monitored. In the first three weeks of this study 25% of all new patients were bilaterally blind (corrected acuity less than 3/60). Similarly, in the first four months of the clinic's operation 33% of all eyes examined had been blind. With this proportion of severe pathology it can be

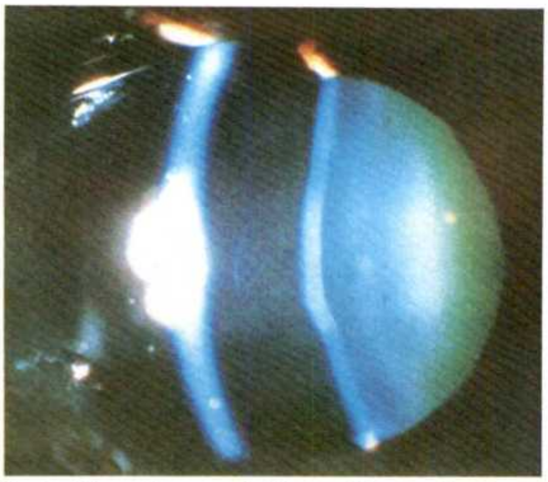

Fig. 2 *Plateau formation in left eye of 79-year-old male, with the pupillary area of anterior lens capsule elevated and protruded forwards, while the centre remains flat. The pupillary zone of capsule has the whitish opalescence of frosting.*

understood that many potential case and control eyes had to be disqualified from further analysis because of additional pathology, such as uveitis, severe glaucoma, or a mature cataract where the details of the lens capsule could not be clearly seen or where it was already wrinkled.

DATA ANALYSIS

Patients with plateau or bag herniation of the anterior lens capsule in either eye were regarded as 'cases' and were compared with controls who did not have such capsule changes. Similarly, eyes with plateau or bagging of the lens capsule were regarded as 'case eyes' and were compared with 'control eyes'. The latter analyses are reported in this paper. Thus the eye is taken as the experimental unit, since each eye is independently classified according to characteristic of primary interest that are local to it, such as climatic keratopathy and anterior lens capsule change. The comparisons were made within strata in which cases and controls were similar in respect of age, sex, and presence of exfoliation. Multivariate log-linear modelling was used to evaluate the inter-

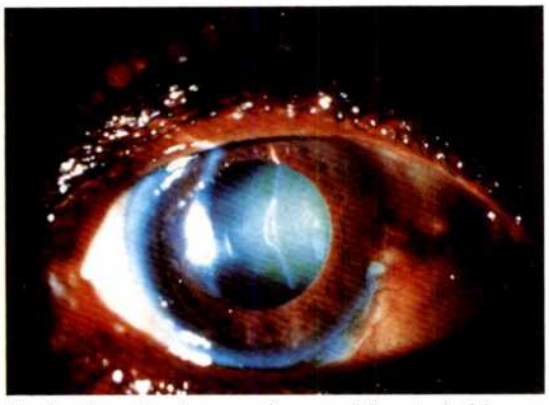

Fig. 3 *Transition between plateau and 'bagging' of the anterior lens capsule. The contour is tending towards anterior lenticonus. Right eye of same patient as Fig. 2.*

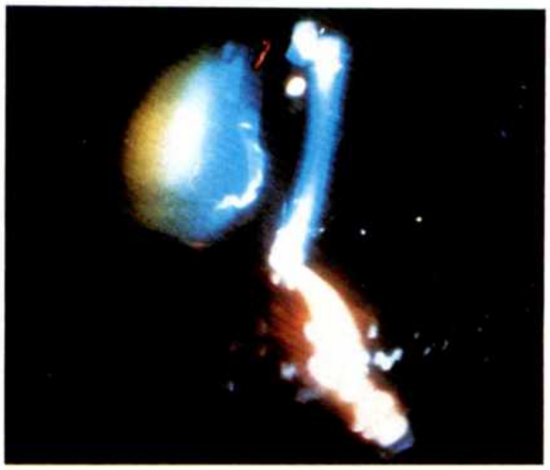

Fig. 4 *'Bagging' of the anterior lens capsule. The limits of the protruding lens are defined by the margin of the undilated pupil. The underlying lens centre is clear.*

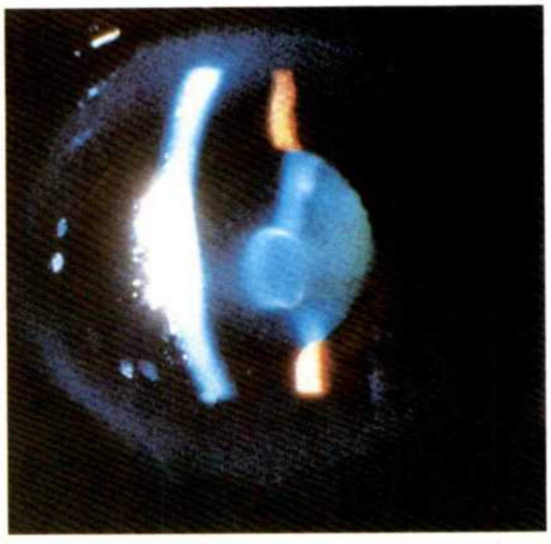

Fig. 5 *Frank herniation of central anterior lens capsule and contents through the pupil in 80-year-old male. The details of iris margin and lens are partially obscured by a fine granular band of climatic keratopathy.*

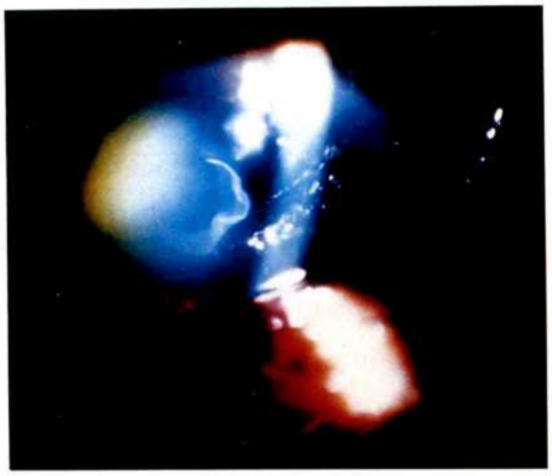

Fig. 6 *Herniation or 'bag' of lens capsule protrusion through pupil, in 55-year-old male nomad. Some of the nodular changes of grade 4 climatic keratopathy are visible.*

relationships between capsule changes, keratopathy, exfoliation, cataract, age, and sex.

The analyses of the association between lens capsule change and keratopathy were performed with both exclusion and inclusion of eyes with intraocular pressure over 25 mmHg, because some authors have considered that glaucoma may itself cause deposition of spheroidal bodies in the cornea or exacerbate existing actinic keratopathy.

Results

The sample comprised 52 patients with plateau or bag herniation of the anterior lens capsule in either eye (cases) and 94 controls who did not have such capsule changes, making a total of 146 patients. The age and sex distribution of the study patients are shown in Table 4.

Table 3 *Definitions of categories of cataract*

*The presence and degree of lens opacities were judged by viewing through a direct ophthalmoscope held close to the patient's eye and against the red glow of the fundus**

1 Normal: No opacities detected

2 Slight: Very early lens opacities such as a solitary radial spoke noted. In other words, it could not be passed as completely normal

3 Partial cataract: An opacity was clearly present but did not obscure all the red glow

4 Complete cataract: No red glow visible. This did not necessarily mean that the cataract was 'mature' in the sense that the white opacities extended up to the anterior capsule when studied with the slit-lamp

*An eye was not included in the analysis if the capsule was wrinkled over a mature cataract.

Table 4 *Age and sex distribution of the study patients*

	Age groups					
	40–49	*50–59*	*60–69*	*70–79*	*80+*	*Totals*
Males	1	17	34	35	15	103
% of total	0·68%	11·64%	23·29%	23·97%	10·27%	69·86%
Females	1	12	18	10	3	44
% of total	0·68%	8·22%	12·33%	6·85%	2·05%	30·14%
Totals	2*	29	52	45	18	146
% of total	1·37%	19·86%	35·62%	30·82%	12·33%	100·00%

*These two patients were both controls and were excluded from analysis as there were no corresponding cases in that age group.

There were 228 eyes in which it was possible to quantify or grade keratopathy, exfoliation, and changes in the anterior lens capsule in each eye. Of these, 68 had plateau or bagging of the lens capsule. The remaining 160 were regarded as control eyes. There were two additional case eyes in which it was not possible to confirm the presence or absence of exfoliation.

Analysis revealed a strong association between capsule change (plateau or bagging) and climatic keratopathy (Table 5).

There was a marked 'dose-dependent' relationship between various grades of climatic keratopathy and

Table 5 *Association of the anterior lens capsule changes with keratopathy. The data are stratified by age and sex. Case eyes are those with plateau formation or bagging of the anterior lens capsule. In this analysis eyes with frosting of the lens capsule are included among the control eyes*

Age		*Males*		*Females*		*Males+ females*	
		No. eyes	*% with kerato-pathy*	*No. eyes*	*% with kerato-pathy*	*No. eyes*	*With kerato-pathy*
50–59	Case eyes	3	100%	1	100%	4	100%
	Control eyes	25	52%	18	33%	43	42%
60–69	Case eyes	20	100%	2	100%	22	100%
	Control eyes	38	61%	32	44%	70	50%
70+	Case eyes	42	100%	2	100%	44	100%
	Control eyes	31	77%	16	63%	47	62%
All	Case eyes	65	100%	5	100%	70	100%
ages	Control eyes	94	64%	66	45%	160	51%

Results of multivariate log-linear modelling:
Significant association between: (a) Capsule change (plateau/bag) and keratopathy; (b) Capsule change and sex; (c) Capsule change and age; (d) Keratopathy and sex; (e) Keratopathy and age.

Age-adjusted odds ratio for sex = 7·6 (95% confidence limits 3·2 and 8), that is, plateau or bagging is about 7 times more common in males than in females of similar age.

The odds ratio for keratopathy in the sample is infinitely high, since every case eye had keratopathy.

NB: Two case eyes in this table are not included in Tables 6 and 7, as it was not possible to confirm presence or absence of exfoliation.

Table 6 *'Dose-dependent' association between anterior lens capsule change and keratopathy Case eyes are those with plateau or bag herniation of the anterior lens capsule. Keratopathy is taken as an index of exposure to ultraviolet sunlight (UV), so that more severe grades of keratopathy indicate correspondingly higher levels of exposure to UV*

	Keratopathy grades (index of exposure to UV)				*Totals*
	*0–1**	*2*	*3*	*4*	
Case eyes	22	7	27	12	68
Control eyes	132	13	13	2	160
Totals	154	20	40	14	228
Odds ratios	1 0	3·2	12 5	36 0	
Test for trend	χ^2=64 1 p<0 001				

Findings indicate strong trend of progressive increase in risk of capsule change with rising level of exposure to UV

The trend persists when the data are stratified by exfoliation

Summary				
Odds ratios	1 0	3 8	10 3	45 6

*Grades 0 and 1 keratopathy are combined in order to avoid infinitely high odds ratios due to zero cell value

changes in the anterior lens capsule. On the assumption that more severe grades of keratopathy indicate correspondingly higher cumulative exposure to UV, there was a strong trend of progressive increase in risk of lens capsule change with rising levels of exposure to UV light. These data are shown in Table 6. Fourteen eyes had intraocular pressure greater than 25 mmHg. When these were excluded from the analyses set out in Table 6, there was very little change in the odds ratios (1·0, 2·9, 16·0, and 40·1) for the different keratopathy grades: the 'dose-dependent' association between plateau and bag formation and keratopathy remained, and the trend persisted when the data were stratified by exfoliation.

A weaker association was found between lens capsule change and presence of exfoliation syndrome (odds ratio 3·8). No significant association was found between exfoliation and climatic keratopathy.

Frosting of the anterior lens capsule in the absence of other capsule changes was positively associated with keratopathy and with exfoliation. However, the association with keratopathy was much stronger than that with exfoliation (Table 7).

A negative relationship was found between cataract and lens capsule change. Eyes with grade 3 or 4 cataract were about three times less likely to have plateau or bagging compared with eyes with grade 0–1 cataract (Table 8).

Table 7 *Frosting of the anterior lens capsule in relation to exfoliation and keratopathy. Eyes with plateau or bagging are excluded from this analysis*

		Keratopathy		
		0–1	*2–4*	*Totals*
Exfoliation present	Frosting	17	5	22
	Capsule normal	10	0	10
Exfoliation absent	Frosting	34	19	53
	Capsule normal	71	4	75
	Totals	132	28	160

Results of log-linear modelling.

(*a*) Strong association between	Frosting and keratopathy (odds ratio=9 5)
(*b*) Weaker association between	Frosting and exfoliation (odds ratio=3 1)
(*c*) No significant association between	Keratopathy and exfoliation

Table 8 *Inverse association of lens capsule plateau or bagging with cataract Case eyes are those with plateau or bagging of the anterior lens capsule*

Age		*Grade 0–1*	*Grade 2*	*Grade 3*	*Grade 4*	*Total*	*% Eyes with grade 3–4 cataract*
50–59	Case eyes	3	0	0	1	4	25%
	Control eyes	22	9	3	8	42	26%
60–69	Case eyes	8	11	1	2	22	14%
	Control eyes	14	22	4	28	68	47%
70–79	Case eyes	5	12	2	6	25	32%
	Control eyes	7	7	8	17	39	64%
80+	Case eyes	2	8	1	8	19	47%
	Control eyes	1	1	2	4	8	75%
Summary odds ratio						Test of trend	
						χ	p Value
Age adjusted		1	1 168	0 331	0-366	10 9	<0 01
Age and sex adjusted		1	1·218	0 432	0-496	5 4	<0 05
Males only age adjusted		1	1 103	0 246	0 307	7 5	<0 01
Females only		Inadequate sample size					

Discussion

From Somalia we have described a condition of the anterior lens capsule in which it either herniates through the pupil as a 'bag', or is elevated in front of the surrounding lens to form a plateau, and which is associated with severe climatic keratopathy. These two conditions frequently occur together without any sign of cataract or other pathology, and yet together may reduce vision to the level of hand movements. If the fundus is examined over the band of keratopathy with a direct ophthalmoscope with the pupil dilated, a perfectly clear view of disc and macula can be obtained The area of protruding capsule appears as a dark ring or round spot against the red glow of the fundus.

This lens distortion is of importance for two reasons: first, as a cause of severe visual reduction due to its optical interference with image formation, and because of the difficulty of knowing the best surgical procedure to adopt; second, because of its theoretical significance.

Similar changes of the anterior lens capsule have been observed by one of the authors among the people with spheroidal degeneration in Newfoundland and Labrador,[2] though only three examples were noted where the deformity was described as a lenticonus or frank herniation in the pupillary area; usually it took the form of a slightly elevated plateau with a frosted surface. Somalia is located just north of the equator, and large areas are covered by sand which in places is highly reflective of sunlight. The traditional way of life is nomadic, and most of the population, even in towns, have spent a large part of their lives as nomads, herding sheep and camels.

Climatic keratopathy is generally more severe in Somalia than in Labrador. It was recorded as the third most frequent cause of blindness (less than 3/60) after cataract and glaucoma among the patients who came in the first four months of the clinic's operation. When the severe grades of keratopathy are associated, as they usually are, with the anterior lens abnormality, it is sometimes difficult to judge by observation whether the cornea or lens is making the greater contribution to visual loss. The corneal deposits may be scraped off or a lamellar keratectomy performed, yet the vision be very little improved because of the underlying capsule deformity. The experience in Labrador was that a perfectly clear corneal graft or a satisfactory lamellar keratectomy sometimes gave a disappointing visual result, interpreted as due to the abnormal shape and surface of the lens capsule.

In Somalia, in cases where the central part of the band of climatic keratopathy is not very dense, it may be that lens extraction is indicated even in the absence of significant cataract. It seems reasonable, however, first to undertake a trial of the visual results of superior optical iridectomy to allow light to bypass the abnormal corneal and lens surfaces. The lens capsules of these Somali patients are abnormally friable compared with other parts of Africa, Europe, or India. The surgeons at the Centre have learnt never to use capsule forceps, only cryoextraction or the tumbling method.

There is considerable circumstantial evidence that climatic keratopathy (primary spheroidal degeneration) is caused by exposure to excessive doses of reflected ultraviolet light.[1,3] The strong association of the anterior lens capsule change with keratopathy suggests that it also could be caused by excessive light exposure. The cornea is known to filter virtually all light of wavelengths under 300 nm. It seems reasonable to think that the shortest of the wavelengths immediately above this, say 300–340 nm, which would be the most biologically active of the remaining wavelengths, might be absorbed in the superficial layers of the lens, in the pupillary area, possibly by the cuboidal epithelium. This would not be surprising in view of the vulnerability of the corneal epithelium to UV light. The high ambient temperatures in the desert regions of Somalia may accelerate any resulting photochemical reaction.

The lens capsule changes are of theoretical importance in view of the extensive research being undertaken into the possible role of ultraviolet wavelengths in the aetiology of cataract. Here we have a condition confined to the anterior surface of the lens, not necessarily associated with cataract, and yet quite probably due to exposure to some of the short wavelengths of light.

Exfoliation syndrome has also been attributed to light exposure.[4] It is extremely common in the Somali population. Although there was some association of exfoliation with lens capsule plateau formation or bagging, there was no significant association of exfoliation with climatic keratopathy.

For the analyses eyes with frosting were included among the controls rather than the cases. At the outset of the investigation it was not clear whether the frosting represented an early sign of exfoliation or was the first step in the process leading to pleateau and bag formation. Since on clinical inspection all the capsules with plateau formation had central frosting, while only a proportion of the exfoliation had frosting, it seems likely that frosting may be a stage in the development of gross anterior lens capsule deformation.

If, as suspected, the lens capsule alteration is caused primarily by ultraviolet wavelengths, both it and the keratopathy would be susceptible to prevention by the wearing of appropriate sunglasses. This has not yet become a practical possibility in the present stage of development of the nomadic population in Somalia.

We thank Dr Mohammed Abukar Shikey, director of the National Programme for the Prevention of Blindness, Dr Henry Macha, Dr Mohamed Ali Odey, and all the staff of Centre Afgooye for their assistance. This investigation was supported by the British Council for the Prevention of Blindness

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An inexpensive method of indirect ophthalmoscopy

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SUMMARY Attention is drawn to the possibility of performing monocular indirect ophthalmoscopy with a pen torch and a condensing lens when facilities for binocular indirect ophthalmoscopy are not available.

Indirect ophthalmoscopy is most commonly performed with a head- or spectacles-mounted source of illumination positioned in the midline of the forehead. Both hands are thus free to hold a condensing lens and to manipulate the lids or a scleral depressor or to make a retinal drawing. In addition the mounted viewing system optically narrows the interpupillary distance of the observer to provide a stereoscopic view of the fundus image.

However, such advantages may not be necessary when the examiner merely requires a wide angle view of the posterior fundus and the equator. In such cases a hand held bright torch and a condensing lens can constitute a readily available system for indirect monocular ophthalmoscopy.

Correspondence to Mr K R Bishai, FRCS Ed.

Material and methods

The examiner holds a pen torch with one hand just above or below the fixating eye, resting the hand against the forehead or cheek bones to maintain steadiness, and projects the light on to the patient's dilated pupil (Fig. 1). The red glow of the fundus will be observed in the pupillary plane. By intercepting the fundus reflex with a condensing lens of appropriate power—for example, aspheric +20 D or +28

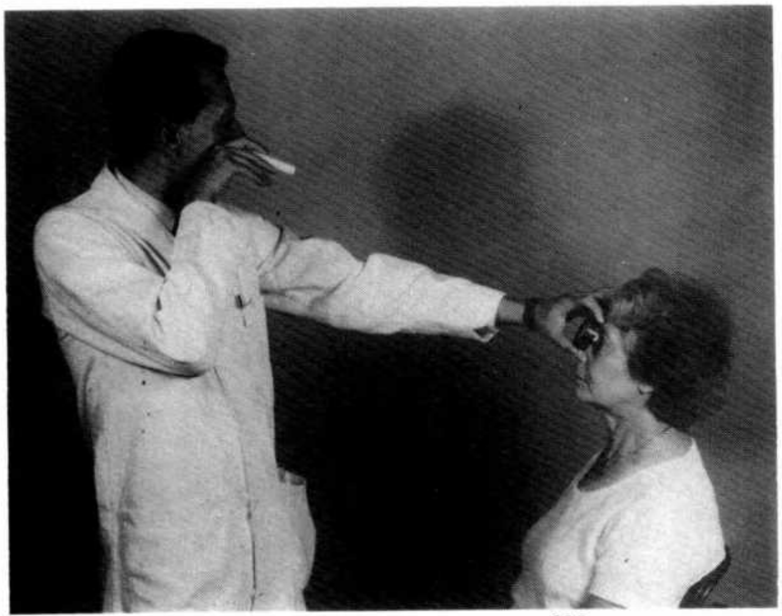

Fig. 1 *Examination of patient by indirect monocular ophthalmoscopy.*

D—a real and inverted image of the fundus will form between the examiner and the patient.

Discussion

The principle of observing the fundus by separating the reflected image from the illuminated beam was first discovered by Purkinje in 1823 and rediscovered independently by Cumming in 1846 and Brucke in 1847.[1] Indirect ophthalmoscopy owes its development to the works of Nagel in 1846, Haab in 1910, and Gut in 1948.[2] Although a number of monocular indirect ophthalmoscopes are still obtainable, its practice has been largely eclipsed by the superior imaging system of the modern binocular indirect ophthalmoscopy.[3]

However, equipment for binocular indirect ophthalmoscopy is cumbersome and not readily available outside ophthalmic departments. Modern pen torches provide a sufficiently powerful source of illumination, enabling ophthalmologists to perform indirect ophthalmoscopy in the absence of better equipment. The emergent monocular image is of adequate quality and will outline gross fundus pathology posterior to the equator. The examination can be performed easily on medical wards or in remote areas where convenient facilities may not be available or serviceable.

I am grateful to Mr I D Berle and other members of the Photographic Department of the London Hospital for their assistance

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Accepted for publication 8 February 1988

Correspondence

Necrotising fasciitis of the eyelids

SIR, A fatal case of this infection, involving a 35-year-old man in Southampton was described recently in your journal by Walters.[1] He has referred to four previously described cases, including two in Southampton, but Carruthers *et al.*,[2] Bahna and Canalis,[3] and Holliman and Catford[4] have described nine others.

The provisional diagnosis of preseptal cellulitis, with erythema and oedema of the right forehead, eyelid, cheek, and neck following a poke in the eye by the patient's daughter, together with purulent discharge from the eye containing Gram-positive cocci (? streptococci) should have prompted the diagnosis of β-haemolytic streptococcal (BHS) or staphylococcal sepsis. Coliform bacteria, as suggested by Walters, are not associated with causing this infection at this site, but can cause necrotising fasciitis of the abdominal wall in association with *Bacteroides* spp following abdominal injury or surgery. The initial drugs of choice are benzylpenicillin in very large doses (20 to 30 megaunits per day intravenously) together with flucloxacillin 4 G intravenously per day until culture results are known Third generation cephalosporins, namely, cefotaxime, together with gentamicin and chloramphenicol, are not indicated, nor is metronidazole, as anaerobic bacteria such as *Bacteroides* spp, fusobacteria, and anaerobic streptococci, which rarely cause this infection originating from an oral focus, are sensitive to benzylpenicillin If the patient is allergic to penicillin, then cephazolin or erythromycin should be used instead.

It is known that sudden death in this infection can occur from disseminated intravascular coagulation (DIC)[5] due to BHS septicaemia, from which the patient probably suffered. Anticoagulation with heparin should be considered in the early stages of management, supported by haematological parameters, and is life saving. The infection spreads rapidly through tissue causing thrombosis of vessels above the fascial layer,[4 5] for which surgical debridement is preferred as antibiotics penetrate into the necrotic tissue with difficulty, reflecting the need for very large doses.

Bahna and Canalis[3] reviewed the literature and recorded early debridement of the eyelid in four out of eight patients, of whom two survived However, more conservative treatment has been pursued by others,[2 4] including ourselves in Southampton,[5 6] when the necrotic tissue of the lid was allowed to form a black eschar over several months in the presence of large doses of penicillin Reconstructive surgery of the lid was still required for loss of tissue and ectropion, but vision was not lost as the globe itself is not usually involved in the infection Blindness has occurred in one patient with this infection, thought to be due to retinal vein thrombosis from pressure of surrounding orbital cellulitis [4] Decompression should be considered in such cases. Walters reviewed debridement at sites other than the eye, where early surgery is recommended, except one case [7]

Early recognition of the clinical features of these infections can be life saving, but fortunately they occur rarely nowadays and the aetiology is often missed. The infection advances rapidly, giving the skin a patchy blue appearance; if blistering occurs it is pathognomonic. Patients also develop toxaemia with a characteristic euphoria and sloughing of the affected part, especially when it becomes anaesthetic Some patients develop early fatal septicaemia and DIC, often occurring over as little as 12 hours, while in others the infection remains localised to necrotic tissue, probably reflecting the host response for both opsonic phagocytosis as well as the propensity for small vessel thrombosis. This type of infection is more common in diabetics and the elderly

BHS group A *(Streptococcus pyogenes)* M type 73 was isolated in pure culture from the blood and lid of Walter's patient. We and others have similarly isolated a pure growth of BHS growth A from four patients with this type of lid infection,[4–7] but, in their review, Bahna and Canalis[3] identified three out of eight patients in whom both BHS group A and *Staphylococcus aureus* were isolated, Carruthers *et al* also isolated this combination.[2] In a rabbit model of this spreading infection[8] we have found synergy between *Staph aureus* or its α-lysin and BHS group A for initiating spread Such initial synergy may occur in humans as well, though *Staph aureus* has only been isolated from 17% of 36 cases.[5] This synergy is missed if the spreading edge of the infection, or the necrotic slough, is cultured rather than the initial site of invasion,[4] ideally, both sites should be investigated The cause of the spreading thrombosis is probably toxin mediated and not due to the inflammatory effect of streptococcal cell walls.[5]

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SIR, Dr David Seal's letter is interesting and comprehensive and I am grateful for the information regarding other cases of necrotising fasciitis involving the eyelids

I would certainly concur with Dr Seal that the β-haemolytic streptococcus is the principal causative organism of necrotising fasciitis and that high dose benzylpenicillin is the treatment of choice (with the support from flucloxacillin as cover against *Staphylococcus aureus*) The choice of antibiotics is easy once the diagnosis has been established and organisms isolated, but I feel that when the patient is first seen and admitted a high dose broad spectrum antibiotic is justified but agree that it should be accompanied by flucloxacillin The diagnosis of necrotising fasciitis is first made on clinical grounds, and it can take 24 to 48 hours for the pathognomonic clinical features to appear. I suspect that many cases are missed I would strongly recommend that, as in this case, the microbiologists are involved from the start and that an opinion should also be sought from one's dermatological colleagues

Disseminated intravascular coagulation (DIC) can indeed occur and cause death but was not found in the patient I described.

One should always watch out for orbital cellulitis when confronted with lid infections. However, my understanding is that necrotising fasciitis is confined to the skin and should not directly affect deeper tissues or penetrate the orbital septum to cause an orbital cellulitis.

I am aware that some cases of necrotising fasciitis of the eyelid have been treated conservatively and that the patient has survived, though requiring reconstructive lid surgery. However, I still feel that early surgical debridement (together with intensive antibiotic treatment) is the treatment of choice provided the diagnosis is established early enough.

I have recently heard of a case in which the affected area of skin was surgically reflected and the deep surface cleaned of inflamed and necrotic tissue. The underlying fascia was also cleaned. The skin was then laid back into position (as per a skin graft with a pedicle) and recovered well This is an interesting approach and may be a way of avoiding the serious cosmetic consequences of excision of a large area of affected facial skin.

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Optic nerve involvement in methanol poisoning

SIR, I was very much interested to read the paper entitled 'Optic nerve involvement in a case of methanol poisoning' by Peter Naeser.[1] This paper contains some serious errors of omission as well as commission To set the record straight, I would like to point these out. They are as follows:

(1) We produced experimental methyl alcohol poisoning in rhesus monkeys and investigated exhaustively the subject of ocular and optic nerve toxicity by conducting detailed clinical, morphological, and biochemical studies on the subject.[3-6] The author makes no mention of our studies at all. Our studies proved that the principal ocular lesion seen in methanol poisoning is the development of toxic optic neuropathy, this contradicts the statement by the author that 'the optic nerve has only infrequently been investigated.' We investigated the optic nerve in detail by light and electron microscopy and found swelling of the oligodendroglial cytoplasm in contact with the axons and of the astrocytes in the retrolaminar optic nerve and the intraorbital optic nerve. We found no vascular lesions in the optic nerve on light and electron microscopy, nor on horseradish peroxidase studies.

(2) The author states that 'The perfusion of the centra parts of the nerve from a central optic nerve vessel with different extension may be of importance.' The author cite a 25-year-old paper by François and Neetens[7] in support o the existence of a central artery of the optic nerve, a few months after that paper[7] was published I[8] pointed out the fallacies in this paper by François and Neetens[7] an disproved conclusively the existence of any such centra artery of the optic nerve, based on my studies[8-10] My detailed studies on the ophthalmic artery[9] and blood suppl of the optic nerve[8-10] (to which the author makes no reference in the paper) showed that no such artery exists in man This finding was later confirmed in studies by several othe authors, including François' own group subsequently,[11-1 when they stated that in their series of 40 optic nerves the did not find any central artery of the optic nerve.[11-13] thought the mythical central artery of the optic nerv expired long, long ago The concept of a watershed zon in the retrolaminar part of the optic nerve, postulated b Rootman and Butler,[15] totally lacks any scientific proof Thus the basic assumptions regarding the blood supply o the optic nerve in this paper are invalid.

It is a tragedy that the subject of the blood supply of th optic nerve has been plagued for decades by a very seriou problem. To explain ischaemic disorders of the optic nerv according to their preconceived theories many authors from time to time have resorted to misstating and distorting th observed facts about the blood supply of the optic nerve to suit their own convenience they have ignored wel established anatomical and physiological facts. To creat anatomy to suit a pet theory instead of vice versa is the exac opposite of scientific inquiry. No matter how often they ar disproved, such pet theories once published, persist lik skeletons which may tumble out of the closet years later like the mythical central artery of the optic nerve, s miraculously resurrected in this paper.

The author, based on one case, implies that optic nerv damage in methanol poisoning is due to vascular disturbance in the optic nerve. Our studies, and those by man other authors, based on much more extensive material, len no support to this view. Thus this misleading paper, in a effort to explain the optic nerve lesions in one case, ignore all the weight of evidence available on the subject o changes in the optic nerve in methanol poisoning and on th blood supply of the optic nerve This seriously undermine its scientific credibility.

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Sɪʀ, Thank you for the opportunity to reply to the query posed by Professor Hayreh.

(1) The statement in my report that 'the optic nerve has only infrequently been investigated' points to the human situation and not to the counterpart in the experimental animals. The lack of registration of the optic nerve changes in humans most likely reflects the insufficient enucleation technique applied in post-mortem examinations, where the nerve is usually cut close to the eye ball and the optic nerve is left in the orbit. It is true that Professor Hayreh and his group in their very thorough morphological investigation of the optic nerves from three rhesus monkeys showed swell-

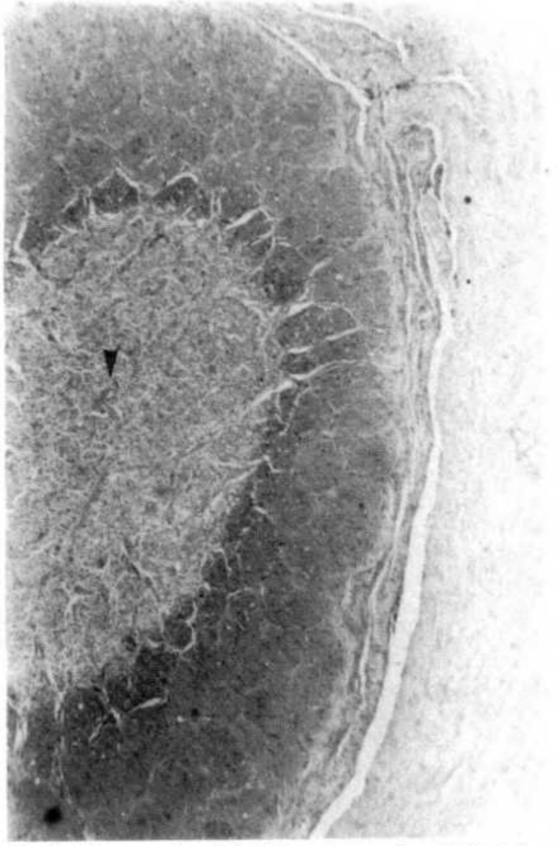

Fig. 1 *Cross section of the left optic nerve 2 cm behind the eye globe showing a central vessel (arrow). (×34).*

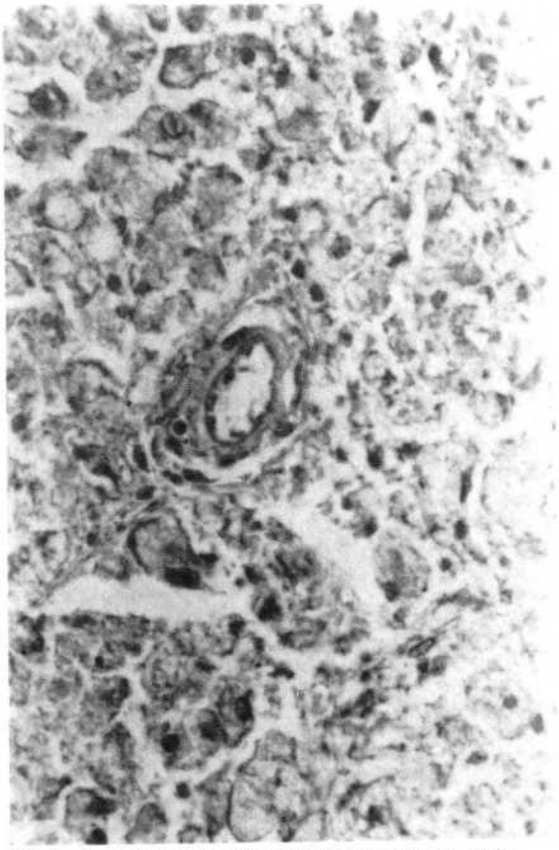

Fig. 2 *Larger magnification from the central part of the nerve with the small artery surrounded by necrotic axons. (×340).*

ing of oligodendroglia and astrocytes in the retrolaminar and the intraorbital optic nerve.[1,2] There is, however, no reference made to the optic nerve morphology within the optic canal or intracranially. Whether the changes are distributed centrally, peripherally, or evenly in the whole transverse sections is not commented on, and it is therefore difficult to compare their results with my observation.

(2) Professor Hayreh furthermore comments that I, in the discussion of my article, mention that 'The perfusion of the central parts of the nerve from a central optic nerve vessel with different extension may be of importance.' In Figs 1 and 2 in this letter, where the micrographs are taken from the left optic nerve 2 cm behind the eye (i.e., the same section as Fig 2E in the article), such a vessel is seen. In the greater magnification the vessel can be identified as a small artery. In my case the central retinal arteries enter the optic nerve bilaterally 1 cm behind the eye, as can be seen on Fig. 2A and 2D in my article. Thus, it is shown that the central optic vessel is posterior to this in the nerve. I think that this finding is difficult to dispute despite the statements given by Professor Hayreh.

Finally I will point out that the finding of bilateral central optic nerve necrosis in methanol poisoning is new. However, its pathogenesis is still unclear.

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Book review

Guide Pratique des Examens de Laboratoire en Ophtalmologie. By S Liotet and Y Morin. Pp 219. 280F. Masson: Paris. 1988.

This is a useful small book designed to aid the ophthalmologist in the choice of the wide and sometimes bewildering array of available laboratory investigative techniques, to acquaint him briefly with the aims, practicalities and limitations of the techniques, and also to help him understand the result as well as prompting him towards further investigation.

The format is succinct. The first three chapters cover the range and applicability of biochemical, microbiological, and cytological techniques, with a large number of clear diagrams illustrating the principles and results of tests and types of cellular abnormality in the case of cytology. This is not a histopathologically orientated text. All chapters and sections are referenced, mostly with recent publications, many in English. The advice is knowledgeable and the book would give reassurance to a clinician lacking in confidence. There are omissions, for example, there is no discussion of techniques to investigate acanthamoebae beyond stating that identification is direct. Conversely the section on sympathetic uveitis reflects the paucity of available methods of diagnosis and recommends examination of the cerebrospinal fluid (and subsequent discovery of a lymphocytosis).

The last chapter is in many ways the most interesting: it consists of an aide-mémoire and checklist of pattern of presentation and investigation of diseases listed by name, including syndromes and as such would aid the harassed or forgetful resident (or consultant)—though one might be discreet in admitting to usage.

The book is the distillate of many years' experience, and I enjoyed it. But it cannot be said to be readable as a whole and is undoubtedly a vade-mecum. Possible purchasers should not be deterred by the fact that it is in French, for the brevity and list format make comprehension easy.

A MCCARTNEY

Notes

Panhellenic congress

The 22nd Panhellenic Ophthalmological Congress will be held in Athens on 25–28 May 1989. The congress will be at the Hotel Caravel, 2 Vas. Alexandrou Street, 116 10 Athens. Full details from the Secretariat, 10 Loukianou Street, 106 75 Athens, Greece. Registration fee after 28 February 1989 $250.

Institute's 40th anniversary

Professor Adam Sillito delivered the Duke-Elder foundation lecture on 4 November 1988 as part of the celebrations commemorating the 40th anniversary of the Institute of Ophthalmology. Under the title 'The eye's way to the brain', he discussed retinal redundancy, synaptic gates, and attention's key to the mind – their implications for neuro-ophthalmology.

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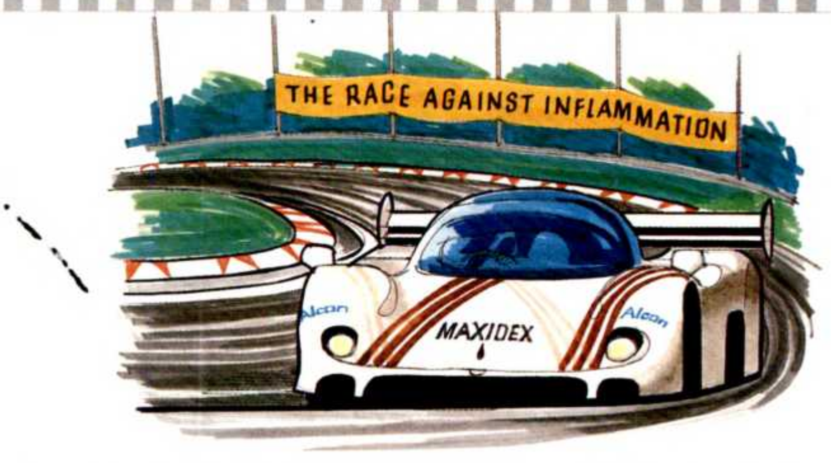

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ABRIDGED PRODUCT INFORMATION

Refer to Data Sheet before prescribing.

USES

Elevated intra-ocular pressure including: ocular hypertension, chronic open-angle glaucoma (including aphakia); secondary glaucoma.

DOSAGE AND ADMINISTRATION

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CONTRA-INDICATIONS

Bronchial asthma, history of bronchial asthma, severe chronic obstructive pulmonary disease. Sinus bradycardia, second- and third-degree AV block, overt cardiac failure, cardiogenic shock. Hypersensitivity.

PRECAUTIONS

'Timoptol' may cause side effects of systemic beta-blockade.

Cardiac failure should be adequately controlled before prescribing. History of severe cardiac disease requires monitoring for cardiac failure and checking of pulse rates. Respiratory and cardiac reactions (including death) have been reported.

Patients receiving a beta-blocker orally and 'Timoptol' may experience an additive effect on IOP or on known systemic effects of beta-blockade.

Rashes and/or dry eyes have been reported with beta-blockers. Reported incidence is small, and most cases clear on withdrawal. If seen, beta-blockers should be withdrawn gradually.

Do not use in patients with soft contact lenses. Mydriasis resulting from use of 'Timoptol' with adrenaline reported occasionally. Potentially, hypotension and/or marked bradycardia may result from addition of 'Timoptol' to a calcium antagonist, rauwolfia alkaloid or beta-blocker.

Children: Not recommended. Data not available for use in children.

Nursing: Mother should either stop nursing or stop 'Timoptol'.

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SIDE EFFECTS

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Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebrovascular accident, cerebral ischaemia, congestive heart failure, palpitation, cardiac arrest.

Bronchospasm (predominantly with pre-existing bronchospastic disease), respiratory failure, dyspnoea. Headache, asthenia, nausea, dizziness, depression. Hypersensitivity, rash, and urticaria.

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BASIC NHS COST

0.25% Ophthalmic Solution 'Timoptol', £5.18 per 5 ml pack.

0.5% Ophthalmic Solution 'Timoptol', £5.82 per 5 ml pack.

PRODUCT LICENCE NUMBERS

0.25% Ophthalmic Solution 'Timoptol', 0025/0134. 0.5% Ophthalmic Solution 'Timoptol', 0025/0135.

Issued July 1988.

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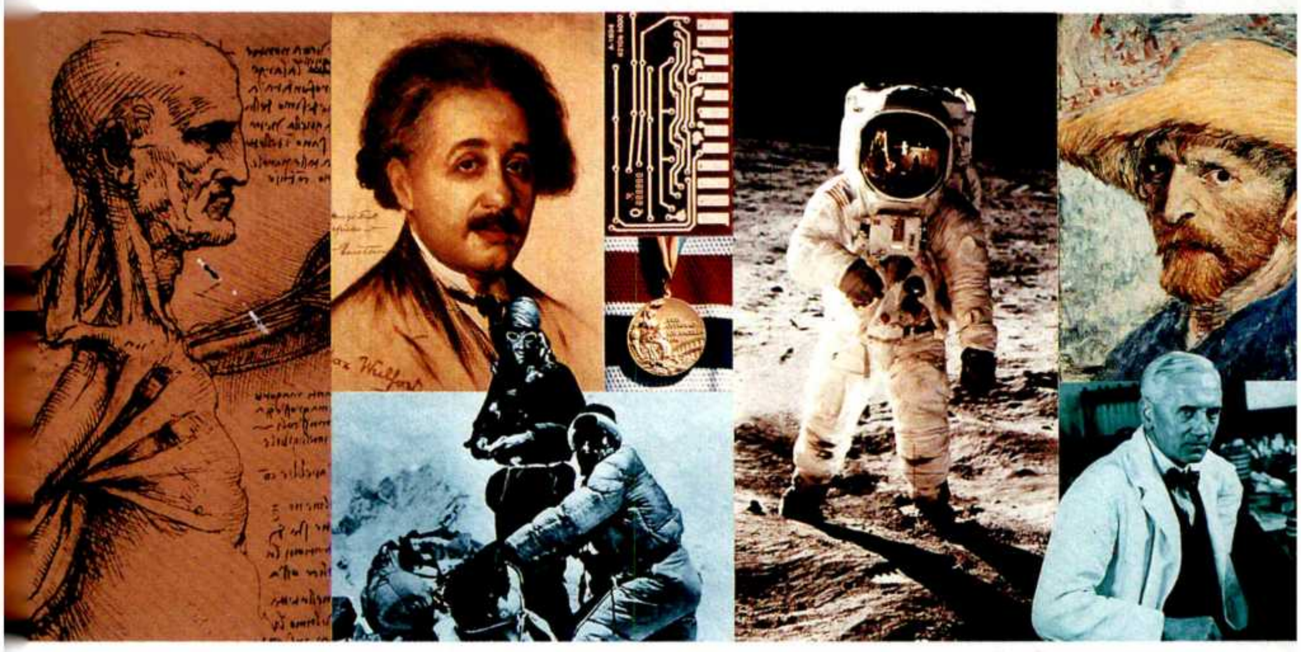

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British Journal of Ophthalmology, 1989, **73**, 241–246

Changes in colour contrast sensitivity associated with operating argon lasers

KEMAL GÜNDÜZ* AND GEOFFREY B ARDEN

From the Department of Clinical Ophthalmology, Institute of Ophthalmology, Judd Street, London, and Electrodiagnostic Clinic, Moorfields Eye Hospital, London

SUMMARY A new test of colour vision using computer graphics has been used to obtain quantitative estimates of colour contrast sensitivity in ophthalmologists before and after they have treated patients by argon laser retinal photocoagulation. The colour vision of all subjects is normal when tested with the 100-hue test and HRR (Hardy, Rittler, Rand) plates, but colour contrast sensitivity measured along a tritan colour confusion line is selectively impaired after a treatment session. No such change occurs after a medical session spent examining patients with a fundus camera. In younger ophthalmologists the sensitivity recovers several hours after the treatment session ends, but in some persons there is a prolonged and possibly permanent elevation of threshold.

In the last decade the use of lasers in ophthalmology has provided some of the most important advances in the treatment of disease. The long-term beneficial effects (especially panretinal photocoagulation in diabetes) of laser therapy[1-3] are undoubted, but there is still some concern about the side effects of the treatment itself. It has been shown that panretinal photocoagulation causes short-term losses in visual acuity and a temporary loss of foveal contrast sensitivity, as well as longer-term side effects.[3-6]

In addition there is of course concern about the safety of the users of medical lasers. Filters automatically protect the ophthalmologist's eye when the viewing beam changes to the coagulating beam. Even so, when the low-power aiming beam is operating, brilliant reflections ('flashbacks') from the plane surface of the contact lens may enter the eye. There have been numerous investigations into the threshold for laser damage to the retina. Any momentary irradiance in the pupil plane exceeding 2·5 mW/cm^2 is considered to be dangerous for bystanders, and this level is found to the side of the contact lens or within 1 m of its front surface.[7] It has been shown that even additive effects of several flashbacks plus the treatment beam (which is considered very safe even for hours of viewing) never exceeds the limit of 10 mJ/cm^2 per day.[8]

We have devised a new method of testing colour vision using a personal computer to drive a colour graphics peripheral and a colour television monitor. The test is an extension of contrast sensitivity testing[9] to the domain of colour. In monochromatic contrast sensitivity tests a grating is presented to the patient, and the minimum degree of luminance contrast which is visible is determined. The computer in this new test calculates the voltages which must be presented to the monitor to produce a grating in which luminance is constant, but in which the colour varies across the screen.[10] The minimum detectable colour contrast is determined. Loss of luminance contrast sensitivity to low spatial frequencies is a very sensitive indicator of visual defects in a variety of neuro-ophthalmological conditions, and losses precede those detectable with ordinary sight test charts. In the same way it appears from our results that colour contrast sensitivity is a method of detecting losses of colour vision when other tests may fail.[6 10-12] Thus the minimal degree of protanomaly which can be detected by HRR plates corresponds to a colour contrast threshold which is over 300% of the average normal mean value, and 250% of the maximum normal threshold.

Some of the reasons for the success of the method are that the grating is presented in the centre of a large uniform field, so that when it is below threshold it is indistinguishable from the field. Thus edge effects and variations of illumination cannot affect the result. The grating also appears in brief flashes—which occupy only 2 TV frames—4 times a second. Thus the test incorporates spatiotemporal factors, which are important in the successful use of luminance contrast gratings[13] and also for the discrimination of colour.[14] Again, the patient's relative spectral sensitivity is determined on the same TV system by heterochromatic flicker photometry before colour vision is tested, so that as far as possible the test colours are accurately isoluminant for each subject: because of differences between individuals, no other test of hue discrimination can rule out clues based on luminance differences. Finally, the test is automated; threshold is repeatedly determined, and the variance of the measurements calculated by the computer, until a reliable result is obtained.

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In producing the test we have calibrated it by determining the thresholds of a number of normal people, most of whom are workers in the hospital. In the course of this we retested a number of the volunteers to discover the short- and long-term reproducibility of the values of threshold. We discovered that some doctors' results showed a considerably greater variability than was the case with most persons, and further investigation showed that this variability was associated with the use of medical lasers. Therefore we specifically measured colour thresholds in doctors before and after they had spent a session using the argon laser. The results indicate that laser usage is associated with a loss of colour contrast sensitivity. Despite the fact that this phenomenon is in most cases temporary, this appeared to us sufficiently important to warrant a preliminary report on a small series.

Subjects and methods

EQUIPMENT

The system consists of a Nimbus microcomputer (Research Machines, Oxford), which drives a Pluto 1 colour graphics system. The latter produces images on an RGB (red, green, blue) colour monitor (Electronic Visuals 5000). The Pluto 1 can display a palette of 256 colours chosen from over 17 million, and the program arranges these to be isoluminant within 1%. The colours are all specified in terms of the CIE* (XYZ) fundamentals. They are used to colour 2 cycles of a square wave grating subtending 0·6 c/degree, which occupies the central 25% of the monitor screen. The surround has the hue of the central colour of the palette. In general the range of hues displayed falls on either a protan, deutan, or tritan colour confusion line ('axis'). There is no generally agreed definition of colour contrast. We have used an operational definition: colour contrast is defined as 0 when all parts of the grating have the same colour, and as 100% when the difference between the colours is the maximum possible with the system. The CIE co-ordinates of these colours are determined by the emissions of the three phosphors.

The colour contrast threshold is measured by displaying a grating in which colour contrast is 0, and gradually incrementing the colour contrast in steps of 1% every second (method of ascending limits). In our standard protocol the grating appears 4 times a second with a duty cycle of 20%, that is, for a nominal 50 ms: during this period the area of the grating is twice briefly excited by the TV raster. The subject sees a grating which repeatedly appears and vanishes: it appears to flash on and off. At threshold neither the colours nor the outlines are distinct; there is only the impression that 'something' is appearing. The incrementation of contrast which occurs every fourth flash also cannot be detected. Thresholds of a number of normal people have been determined, including spouses and accompanying persons in a glaucoma clinic, and the normal colour contrast threshold has been found to be 4·5%, with a range from 3 to 7%: similar thresholds are found for colours which lie along protan, deutan, and tritan axes. In cases of eye disease a loss of colour contrast sensitivity along a single one of these axes can frequently be observed. This is convenient, since a normal result (achieved along the protan axis, for example) indicates that psychological variables are not affecting the determination of threshold. Therefore a loss in a different axis, even though the threshold is only marginally above the upper limit of normal, is an indication of disease. Further details are given elsewhere.[10-12]

SUBJECTS

Consultant surgeons and residents of the Retinal Diagnostic Department of Moorfields Eye Hospital who are involved in the treatment of large numbers of diabetic patients were tested before and after they had finished a session (nominally 3·5 hours) of treatment by standard panphotocoagulation. Usually these were morning sessions, so measurements were made before 9 am and in the early afternoon. As controls we used members of the Medical Illustration Department, because these persons do fundus photography and fluorescence angiography on the same patient population. They use fundus cameras, slitlamps and ophthalmoscopes, so their work involves the use of similar viewing devices, during which the operator sees bright flashes from the sources used to illuminate the patient's retina. Thus the work of the control group was matched as closely as possible to that of the laser users. Table 1 gives the ages of the

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Table 1 *Ages and experience of subjects tested*

	Laser operators		*Medical photographers*	
	Age	*Has used equipment for (years)*	*Age*	*Has used equipment for (years)*
1	34	1	40	20
2	38	3	22	4
3	33	1	22	5
4	51	15	33	8
5	36	4	58	32
6	33	5	52	27
Age (mean with SD)·	37 5 (6 9)		37 8 (15·1)	

Table 2 *Test-retest variability in two subjects; showing the diurnal variation in one following exposure to laser light. The measurements of colour contrast sensitivity were made along the tritan colour confusion line*

Measurement on day number	*am* *Contrast threshold (mean and SD) (percent of maximum)**	*pm*
Non-user of laser		
1	4 8 (0 2)	5·1 (0·2)
2	4·9 (0·2)	5·2 (0·1)
3	4 7 (0·1)	5·0 (0·2)
4	4·7 (0·3)	5·0 (0·3)
5	4 9 (0 2)	5·2 (0 2)
Average of results	4·8 (0·2)	5·1 (0·2)
Mean difference between am and pm thresholds 0·3 (0·0)		
Laser operator		
1	6·4 (0·2)	8·8 (0·2)
2	6 2 (0 2)	9·1 (0·3)
3	6·5 (0·3)	9 9 (0·4)
Average of results	6 4 (0 2)	9·3 (0·3)
Mean difference between am and pm thresholds 2·9 (0·5)		

*Average normal result=4·5 Maximum normal result=7 0

subjects, and the time for which they had been engaged in the intensive use of lasers or had used the fundus cameras on a daily basis. None of those subjects had ever experienced an incident in which a laser was used incorrectly or had used a laser in which there had been any optomechanical failure (but see below).

LASERS

A Lasertek 41 AK and Coherent 900 are in use at Moorfields.

Both blue and green lines are employed in these lasers. We have also tested visiting ophthalmologists, and we have no reason to suppose that the model of laser used has any bearing on the results shown below. The light outputs of the Moorfields lasers are monitored by the makers and by the Laser Safety Officer. A radiometer (EE & G Ltd) placed at the eyepiece of the binocular microscope recorded 40–90 $\mu W/cm^2$.

OPHTHALMIC TESTING

All the persons tested had a corrected acuity of 6/6 or better, and none had any ocular or systemic abnormality. All had recently been investigated with biomicroscopy. All had had ocular vision tests with HRR plates or the 100-hue test, and no test result was abnormal.

Results

Table 2 shows the results which drew our attention to the phenomenon we report.

The test-retest results from a normal observer are shown for a period of five days. The subject was tested twice daily for all colour combinations, but only the results on the tritan axis are shown (the others are comparable). The thresholds (expressed as a percentage of the maximum colour contrast obtainable—see 'Methods') show that the variability of threshold was small in a trained observer. Since the minimum increment of colour contrast is 1%, the subject evidently always responds when the colour contrast has been incremented either 4, 5, or 6 times from the zero condition. The slight but non-significant increase in threshold determined in the afternoon implies that the probability that he responded to the 6th increment was slightly higher at the end of the session.

The results for a laser user are shown below. He was tested only in the tritan axis. Note that the mean level in the morning was higher for this subject, but the thresholds were within normal limits. The reproducibility of the threshold in the morning before the laser was used in also impressive. The three readings were obtained on three separate occasions, spanning three months. Following the use of the laser the threshold was higher and above the highest value (7·0) found in other normal subjects, but again thresholds on three afternoons were very similar. The difference between morning and afternoon sessions is significant, but not highly (t=10·0, n=3), and it is possible that this subject had an unusual circadian change in colour contrast threshold.

Therefore additional observations were made with a group of six users of lasers, matched with other hospital employees, whose work consisted of repeated funduscopy and the use of bright lights (Table 1). The results are shown in Table 3. In these subjects only one set of measurements was made, but thresholds were determined along protan, deutan, and tritan colour-confusion lines. As will be seen, the first two measurements provide a useful additional control.

Inspection of Table 3 shows that before the session

Table 3 *Thresholds before and after a working sessions (mean and SD)*

Protan				*Deutan*				*Tritan*			
Laser users		*Others*		*Laser users*		*Others*		*Laser users*		*Others*	
Before session	*After session*	*Before session*	*After session*	*Before session*	*After session*	*Before session*	*After session*	*Before session*	*After session*	*Before session*	*After session*
5·6 (0·8)	5·5 (0·2)	4·5 (0·5)	4·8 (0·5)	5·3 (0·3)	5·3 (0·1)	4·8 (0·3)	4·9 (0·3)	5·0 (0·3)	6·3 (0·6)	6·5 (0·5)	6·7 (0·4)
7·2 (0·3)	9·0 (0·1)	5·4 (0·3)	5·7 (0·5)	7·7 (0·4)	9·2 (0·3)	5·3 (0·4)	5·9 (0·5)	8·5 (0·3)	13·5 (1·3)	6·6 (0·4)	6·7 (0·4)
6·2 (0·2)	6·2 (0·2)	5·4 (0·3)	5·7 (0·3)	6·0 (0·2)	6·9 (0·2)	5·2 (0·4)	5·6 (0·5)	6·4 (0·2)	8·8 (0·2)	6·4 (0·3)	6·8 (0·1)
8·3 (0·4)	9·8 (0·4)	4·5 (0·3)	4·5 (0·3)	8·8 (0·8)	10·2 (0·7)	4·6 (0·2)	4·9 (0·1)	12·2 (0·9)	12·8 (0·6)	4·7 (0·2)	4·8 (0·1)
8·1 (0·4)	8·2 (0·6)	5·4 (0·4)	5·5 (0·4)	8·3 (0·4)	10·3 (0·7)	5·2 (0·3)	5·6 (0·4)	10·0 (0·5)	13·0 (0·8)	5·5 (0·3)	5·7 (0·4)
5·5 (0·4)	5·9 (0·3)	6·1 (0·3)	6·3 (0·4)	6·1 (0·3)	6·0 (0·1)	6·2 (0·2)	6·4 (0·2)	6·1 (0·2)	6·9 (0·1)	6·3 (0·4)	6·6 (0·3)
Mean values of the groups				Mean values of the groups				Mean values of the groups			
6·8 (0·4)	7·4 (0·3)	5·2 (0·4)	5·4 (0·4)	7·0 (0·4)	8·0 (0·4)	5·2 (0·3)	5·6 (0·3)	8·0 (0·4)	10·2 (0·6)	6·0 (0·4)	6·2 (0·3)
Mean of differences between 'before' and 'after' session test				Mean of differences between 'before' and 'after' session test				Mean of differences between 'before' and 'after' session test			
0·63 (0·81)		0·1 (0·23)		0·95 (0·85)		0·3 (0·17)		2·18 (1·66)		0·22 (0·17)	

Significance of statistics

t *Test between*	*Protan*	*Deutan*	*Tritan*
Laser user/non-laser user	$p=0·02$	$p<0·01$	$p<0·001$
Before/after session (laser user)	NS	NS	$0·02<p<0·05$
Before/after session (non-laser user)	NS	NS	NS

the non-users of laser had values (mean 5·2%) similar to those previously reported. The results along protan and deutan colour confusion lines given by the laser users were slightly higher than the corresponding values for non-users of laser. Although the mean result is just within normal limits, subjects 4 and 5 had values that initially slightly exceeded any of those found in the normal population. The mean tritan value of the laser users was initially higher than the upper limit of normal, and some of the individual

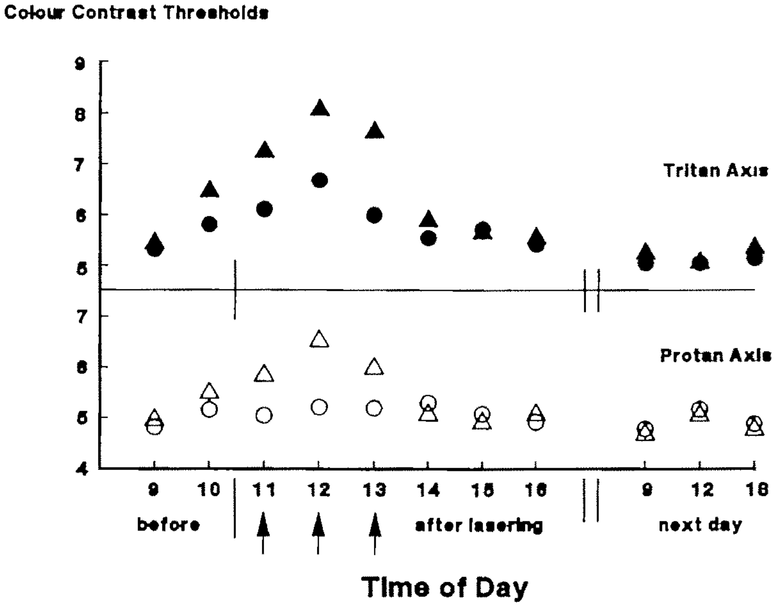

Fig. 1 *The relationship between colour contrast thresholds (ordinate) and use of the argon laser (abscissa). The results from the right eye are given by circles and the left eye by triangles. Colour contrast thresholds are expressed as a percentage of the maximum colour separation possible The upper limit of normal=7 for both protan colour confusion line measurements (open symbols) and for tritan measurements (filled symbols). The subject used his left eye to view the right eyepiece of the binocular, so that it received 'flashbacks', while with the right eye he could see (round the side of the biomicroscope) the reflections from the photocoagulating beam. Groups of 100 laser burns were given at the arrows It is the left eye in which the threshold elevations occur. Note that the effect of the laser is more pronounced for the tritan (blue-yellow) colours, and the effect takes 1–2 hours to reverse Measurements taken on the following day show the result is not due a circadian phenomenon*

results were very high indeed. While it is statistically very probable that the laser users differed from the remainder in respect of the initial protan and deutan results, it is evident that there was an additional loss, confined to the tritan axis only, which cannot be explained on the basis that the test was not performed adequately by the surgeons: for the protan and deutan results were not nearly so high. There appears to be a real, selective loss of blue-yellow colour contrast which cannot be explained by any systematic difference between the surgeon and control groups.

After the session results given by the non-users of laser have changed very little. Thus, if there is a circadian effect or an effect of fatigue, it is reasonable to assume that it is no more than 0·2–0·3 percentage units. The protan and deutan results of the laser users showed increases which were larger but not grossly different from those of the controls—0·6 and 0·95 for the two axes. For the tritan results the increase was much greater—2·2%. The person with the highest initial threshold showed the smallest increase, and therefore the mean of the increases of threshold (mean of the individual differences between the findings before and after the session) has a fairly large variance. It appears likely that during the session laser users experienced further losses in blue-yellow contrast sensitivity. In this context it is understandable that the person with the severest initial loss experienced the least additional loss.

If the results shown in the tables indicate that the use of the laser causes a change in threshold, the change ought to be progressive with continued use. For this reason we simulated the clinical use of the laser by placing a plane surface in the place of the eye and viewing it through one of the standard lenses with the biomicroscope. In one case a dark blue piece of card was used and in another a matte black card. In both cases the light reflected from the surfaces was less than from the normal fundus. The subject's colour vision was tested in the usual way, and then he made a series of 100 burns on the card as quickly as possible (0·4 w, 0·1 s, 500 μm spot size), and colour vision was immediately retested. In one experiment (on KG, see Fig. 1) the subject used his left eye to view the card through the right eyepiece of the binocular: thus it was exposed to all the 'flashbacks', but during the photocoagulating pulses no argon light entered his eye. The right eye on the other hand received no flashbacks but during the photocoagulating pulses saw some fraction of the intense argon light reflected from the card, the contact lens, and the subject's own hand.

It can be seen from Fig. 1 that colour contrast threshold along a protan colour-confusion line may change slightly as a result of the use of the laser, but only in the eye which receives the flashbacks. Similar results were obtained (but not illustrated in Fig. 1) for deutan colours. For the tritan (yellow-blue) grating, using the laser caused a larger change in threshold, which rose above the upper limit of normal in the eye which viewed the flashbacks. Smaller changes occurred in the fellow eye. Colour thresholds remained elevated for over 2 hours. Further measurements were taken the following day. There was no hint of any circadian rise of threshold toward midday.

This experiment was partially repeated on another observer, who held the contact lens centred in the optic pathway, so that its front plano surface was (as near as possible) normal to the optical pathway. This increased the frequency of flashbacks. After a period of 100 burns the subject's threshold rose to above normal, and after 300, delivered as fast as the laser allowed, it more than doubled. The subject was aware that colour contrast threshold in his foveal region had risen above the level in the surrounding peripheral retina, so he had a relative blue-yellow scotoma, and that the major source of light was the flashbacks. He declined to continue the experiment.

ADDITIONAL OBSERVATIONS

We have measured colour contrast sensitivity after light-adapting the eye with bright photographic flashes that bleach most of the rhodopsin in the retina. These are used routinely to achieve a high level of light adaptation prior to measuring dark adaptation. They do not cause a loss of colour contrast sensitivity lasting for long enough to show on our test. We have tested one ophthalmologist who used an argon laser in which the protecting filter failed to cover completely the viewing path when the coagulating beam was employed. As a result the doctor experienced an after-image of some days' duration. A year after this incident colour contrast thresholds were normal and equal in the two eyes for all colour confusion lines. There was no tritan elevation. We have tested several visiting ophthalmologists from two centres on the continent. In two cases of persons over 40 years of age, one from Italy and one from Denmark, who had used argon lasers on a daily basis for several years, tritan colour contrast thresholds were elevated (as in Table 3), though the doctors had not used the laser for several weeks.

Discussion

Colour contrast sensitivity measurements are a new way of assessing colour vision. The test-retest reliability of our system, both in general and in the results shown above, is such that the elevations we see in the surgeons tested cannot be ascribed to normal variation. Again, the elevations are much more marked for one particular colour confusion line, as is often the case in acquired disease, and therefore cannot be considered as part of the population variation. We have also conducted experiments which show that the threshold elevation is progressive, and threshold varies with the length of time the laser is used. We have shown that circadian changes cannot be implicated and that the losses seen are not found in a group of hospital workers who use the same types of equipment (and which deliver intense flashes to the patients' eyes) but who do not use lasers. Therefore we can be sure that general fatigue cannot explain our results. It appears that there are losses of colour contrast sensitivity associated with the use of lasers. Although the series is small, we believe that the loss is greatest in the persons who have used the lasers longest.

If the loss is associated with the use of lasers, is it caused by laser light or by some undefined factor? The results shown in Fig. 1 suggest very strongly that the flashbacks cause the threshold elevation, and a body of evidence indicates that blue light is an especial hazard. Our interpretation of the results is that in argon laser users so much blue light enters the eye that blue cones are selectively affected and colour contrast threshold rises, and recovers slowly. As the years go by, the recovery slows down, till a semi-permanent elevation of threshold results.

Hawerth and Sperling[15] have shown that blue light causes irreversible colour vision defects in monkeys. Marshall[16 17] has calculated that the intensity of light entering the laser users' eyes is approximately equal to that used by Hawerth and Sperling. After exposure to lesser intensities of blue light there is a transient increase in threshold, and Zrenner[18] has used this fact to develop a clinical test. Our results are not necessarily in conflict with those of Sliney and Mainster,[7] who have recently calculated that blue argon light should not be damaging to the laser user's eye. Estimates of damage are derived from assessment of histological lesions in monkeys. There is no evidence that any of our subjects had such lesions, and indeed all tests of vision and colour vision (except our new test of colour contrast sensitivity) have failed to show any visual defect at all.

However, our measurements suggest that repeated exposure to levels of blue argon light may slowly cause small losses of colour contrast sensitivity along an appropriate colour dimension, which may be irreversible or slow to recover. There is no reason why such losses should be associated with other visual impairment: the blue cones are thought to contribute little to visual acuity or to the detection of luminance. However, if further work confirms that even minor changes occur in ophthalmologists' eyes, it is likely that there would be pressure for the redesign of medical laser systems

We thank the consultants and resident staff of the Retinal Diagnostic Department and Medical Illustration staff for participating; and Mr C R Hogg, who provided technical support; the Laser Safety Officer of Moorfields Eye Hospital (Professor J Marshall) for providing evidence about the calibration and maintenance of lasers KG held a British Council Fellowship. The work was supported by a Wellcome Trust grant to GBA.

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Non-contact tonometry in the postoperative eye

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SUMMARY The Keeler Pulsair non-contact tonometer was compared with the Goldmann applanation tonometer in a series of 48 eyes after operation. A correlation coefficient of 0·92 ($p<0·001$) was found between the two instruments, with the Pulsair having a statistically significant tendency to overread the Goldmann slightly in this situation. The Pulsair was, however, shown to be effective in the identification of postoperative ocular hypertension with a high degree of sensitivity and specificity and good patient compliance, while reducing the risk of cross infection.

Most surgeons routinely measure the intraocular pressure (IOP) after intraocular procedures to detect abnormally high or low pressures. Applanation tonometers (AT) indent a known area of the cornea, and when the correct indentation is observed the pressure resisting indentation equates to the force applied, resulting in an estimate of the intraocular pressure.[1]

The Goldmann AT has become the standard instrument used for this purpose and requires a slit-lamp to obtain readings. The Perkins hand held AT operates on a similar principle, and both instruments require the instillation of a local anaesthetic/fluorescein combination prior to contact with the globe.

Non-contact tonometers (NCT) use a puff of air to create an applanation event on the cornea, the changes in the characteristics of the corneal light reflex so produced being measured electronically. This is achieved in the Pulsair NCT by a quantification of the alteration in the corneal reflection which falls on to light sensitive diodes within the instrument. The instrument senses when correct alignment with the cornea has been made by the operator and automatically fires the test pulse, which is approximately half the pressure produced by conventional NCTs (manufacturer's data). A digital readout gives the IOP. No anaesthetics or dyes are required in NCT, and this has led to these instruments being widely accepted by optometrists for glaucoma screening.

In view of the potential advantages of the no-touch NCT method of IOP estimation in the postoperative patient a study was designed to compare the use of the Keeler Pulsair NCT with the Goldmann AT.

Material and methods

A series of 45 patients (48 eyes) under the care of five surgeons were recruited for the study. Each eye had undergone a single intraocular procedure within 24 hours of the IOP measurements being taken. The operations were as follows: 37 cataract extractions (34 with IOL), seven peripheral iridectomies, and four trabeculectomies. Forty-two patients had one eye operated upon and three had both. Each eye had four readings taken with the NCT, the mean of the four being used in the correlation statistics. All readings were taken by the same operator (SAV) with the patients seated. A test pulse was demonstrated on the patient's cheek prior to the intraocular pressure recordings (Keeler have recently incorporated this suggestion into the operator's manual for the Pulsair). Goldmann AT was then performed within five minutes of the last NCT recording by an experienced operator who was unaware of the NCT result.

After the tonometry the patients were asked to state which of the two methods they preferred.

Results

Fig. 1 indicates the correlation of individual NCT means with AT readings, the line on the scatter diagram being a regression line. The correlation coefficient (r) at 0·92 is statistically significant at the $p<0·001$ level (Student's t test). The regression analysis equation indicates the degree to which the NCT tends to overread the AT. Fig. 2 shows this in

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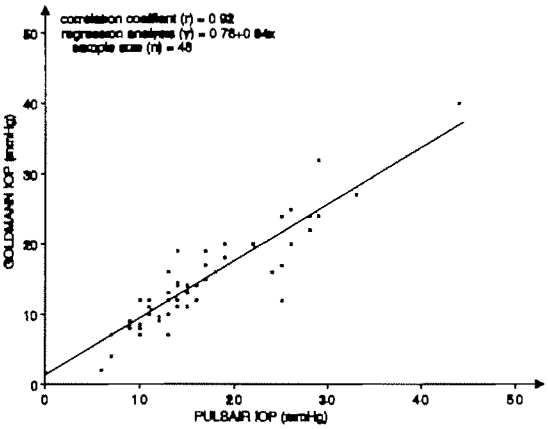

Fig. 1 *Scatter diagram of applanation tonometer (Goldmann) IOP against mean non-contact tonometer (Pulsair) IOP.*

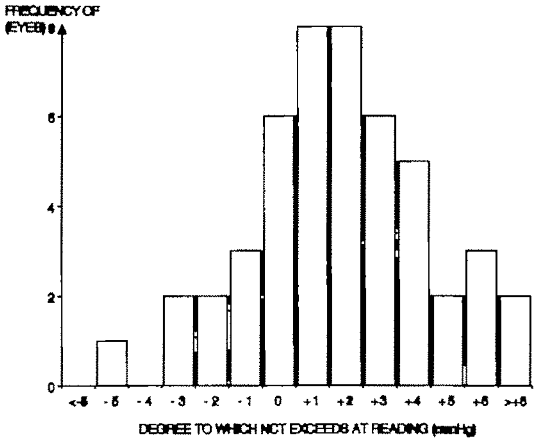

Fig. 2 *Frequency histogram: Non-contact tonometer minus applanation tonometer in 48 eyes.*

an alternative way by means of a frequency histogram. The NCT in postoperative cases has a statistically significant tendency to record a higher IOP than the AT (0·01>p>0·001 by χ^2 test).

If the Goldman AT is accepted as the standard in tonometry, NCT sensitivity in screening for postoperative ocular hypertension can be defined as the number of true positive identified by the NCT (no of eyes in which AT and NCT read >21 mmHg) divided by this number plus those falsely identified as negative by the NCT (eyes in which AT >21 mmHg and NCT <22 mmHg). NCT specificity is defined as the total number of negatives correctly identified by the NCT (AT and NCT <22 mmHg) divided by this number plus those falsely identified as positive by the NCT (AT <22 and NCT >21 mmHg).

The NCT recorded 13 eyes with an IOP >21 mmHg (27%), whereas the AT recorded eight (7%) over this level. All of the eyes which recorded >21 mmHg on the AT recorded >21 mmHg on the NCT (100% sensitivity). Five eyes recorded >21 mmHg on NCT when the AT reading was <22 mmHg (88% specificity), but in none of these did the NCT measure over 25 mmHg.

Ten of the 45 patients preferred the NCT, seven the AT, and 28 had no preference (no significant difference). It should be pointed out that all patients had had Goldmann AT at least once prior to surgery, whereas no patient had experienced the Pulsair NCT before the study. Although no record of the time taken to achieve the measurements was made, the four NCT readings usually took about 30 seconds to complete, and this was often considerably quicker than the AT.

Discussion

Most surgeons routinely measure the IOP after intraocular procedures to identify ocular hyper- or hypotension. An early postoperative rise in IOP commonly follows cataract surgery,[2] and the IOP measures >30 mmHg at 22 hours after surgery in 8% of extracapsular procedures even without the use of viscoelastic materials.[3]

Viral diseases may be transferred by AT,[4-6] and NCT avoids the ever increasing risk of cross infection by the AIDS virus, which is known to be present in the tears of infected individuals,[7] as no patient contact is necessary to perform the test.

The IOP measured with the Pulsair NCT has been designed to equate with the Goldmann AT over a range of 5 to 50 mmHg, with a correlation coefficient of 0·95 and a regression equation indicating a slight tendency to underread the Goldmann AT (manufacturer's data). These results were obtained with unoperated eyes.

It would appear from our study, the first to compare an NCT with an AT in the immediate postoperative period, that in this situation the Pulsair NCT has a statistically significant tendency to read higher than the Goldmann AT.

Postoperatively the IOP is often more difficult to measure accurately with the AT because of a number of factors. These include lid oedema, usually requiring manual elevation of the lid, increased tear film meniscus, and patient non-compliance. These factors may lead to an underestimation of the IOP by AT.

Momentary fluctuations in IOP result from changes in intraocular volume as a result of vascular pulsations associated with cardiac and respiratory cycles.[8] The NCT samples these cycles, taking only milliseconds to record the IOP, and repeated readings do not reduce the recorded IOP.[8] The steady state, however, is disturbed by the AT, which 'damps' the cycles. Repeated measurements reduce the IOP,[9] and the reproducibility in non-operated eyes is to ±2 mmHg in only 65% of cases.[10]

The Pulsair measures the IOP only when the correct alignment has been made with the cornea as detected by light sensitive diodes receiving reflected light from the corneal surface, and, as no extraneous pressure is applied to the eye or adnexa, it measures the IOP at the moment the pulse is activated. With this and the high correlation coefficient in the non-operated eye in mind, it may be that the NCT measures the IOP more accurately than the AT in postoperative cases.

Most surgeons would be unlikely to intervene in the immediate postoperative period unless the IOP rose above 25 mmHg, as most cases of ocular hypertension of this order of magnitude will resolve spontaneously within the next 24 hours with no sequelae. If the Pulsair NCT had been the only screening tonometer in this study, and only readings above 25 mmHg on the NCT had been taken as significant, all eyes measuring >21 mmHg on the AT would have been identified and none would have been missed. AT could then have been used to confirm the NCT result, if indeed this was considered necessary, before intervention.

This study therefore suggests that the NCT, with its associated low cross infection risk, may be used to screen for postoperative ocular hypertension with high sensitivity and specificity and good patient compliance.

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Leber's congenital amaurosis—a new syndrome with a cardiomyopathy

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SUMMARY Seven members of four families had nystagmus noted by 4 months of age, poor vision, photophobia, and a markedly reduced or absent electroretinogram. Six of these patients had a life threatening episode of cardiac failure in infancy. There were also two neonatal deaths, and one of the affected children died at 2 years and one at 19 years. The five surviving children are well, remain with nystagmus, and have visual acuities of less than 6/60, with the eldest two having lost perception of light. They have a short obese habitus distinct from that of their unaffected siblings and parents.

Leber's congenital amaurosis (LCA) is a heterogeneous group of conditions[1] having in common the features originally described by Leber in 1869.[2] Leber noted reduced vision before the age of 1 year, nystagmus, and poor pupillary reactions with the eventual appearance of degenerative changes in the fundi. The inheritance is thought to be autosomal recessive.[1-5] Leber subdivided the condition in 1916 into a simple ocular form and one combined with mental retardation.[6] In 1954 Franceschetti and Dieterle noted the markedly reduced or absent electroretinogram (ERG).[7] The criteria for the diagnosis are now: a profound visual defect from birth, a markedly reduced or absent ERG, and a normal fundal appearance or a retinal dystrophy.

Specific disorders such as infantile or late Batten's disease (neuronal ceroid lipofuscinosis),[8] peroxisomal disorders (such as Zellweger syndrome[9] and infantile Refsum's disease[10]), and mitochondrial cytopathy[11] need exclusion, but their difference from LCA is usually clinically evident. There may be cases of cone dysfunction syndromes or congenital stationary night blindness[12] within any group of patients initially diagnosed as LCA, in particular among those with relatively preserved vision. Appropriate electrophysiological studies will exclude these but should be repeated.

The commonest fundus abnormality in LCA is thinning of the retinal arterioles and a granular retinal pigment epithelium.[3] The appearance of the fundus has also been normal,[13 14] or shown macular 'colobomas',[15] peripheral white dots,[14] nummular pigmentation,[16] granular macular pigmentation, and

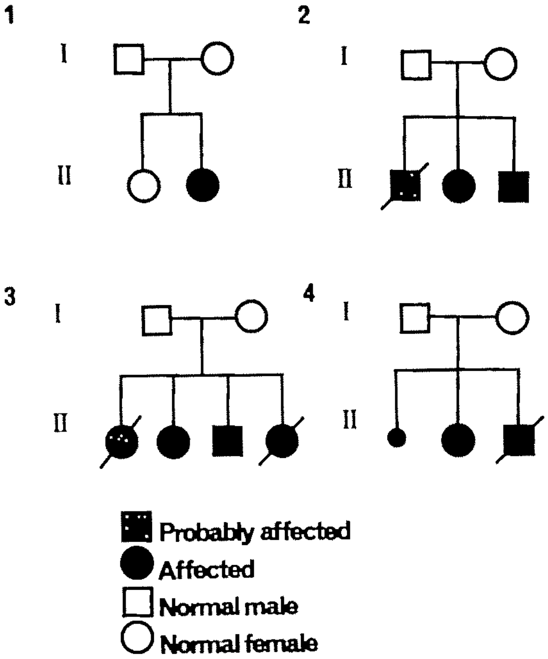

Fig. 1 *Pedigrees.*

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pseudopapilloedema.[17] Cataracts and keratoconus[1] and hypermetropia may be found, and LCA has been described in association with a saccade palsy[18]; this may be a variant of Joubert's syndrome with retinal dystrophy.[19]

The systemic associations described include mental retardation,[3-5 20-22] seizures,[22] deafness,[23] EEG anomalies,[3 21] CT scan changes,[20] and renal abnormalities,[24 25] which may be associated with skeletal malformation[26] or endocrine dysfunction,[27] suggesting a multisystem disorder. There is still value in keeping these patients within the LCA classification, as their initial presentation with an uncomplicated ocular problem does not permit differentiation from classical LCA. In some family members renal function may remain normal unless it is severely stressed, as by an episode of dehydration. In all studies reporting systemic abnormalities, their incidence is probably influenced by the referral pattern.

We now report the association of LCA with acute cardiac decompensation in infancy, which appears to carry a good long-term prognosis for the survivors. We describe seven cases from four families.

Case reports

CASE 1. II 2

This is the second daughter of normal parents. Her elder sister is also healthy. At 3 months of age nystagmus was noted and poor vision suspected. At 7 months while attending hospital for investigation she collapsed with severe cardiac failure due to a cardiomyopathy (possibly viral), which responded to medical therapy. Viral antibody titres were normal and no congenital structural or vascular cardiac abnormalities were found.

There were +9·00 dioptres of hypermetropia, narrow retinal arterioles, and absent electroretinograms (ERGs) from both eyes. At aged 2½ years she was well on digoxin and diuretics, and echocardiography showed improvement in left ventricular performance. Paradoxical pupil responses were noted. Aged 3 years she can identify the 6/60 letter at 2 metres binocularly. Off all medication, her exercise ability is limited only by visual handicap. Cross sectional echocardiography shows mild dilatation of the left ventricle, with a shortening fraction of 39%. The electrocardiogram shows minor abnormalities of the repolarisation phase. Intellectual achievement is as yet uncertain, but development may be delayed even for a visually handicapped child. Her height is on the 90th centile, but her parents are tall. Her weight at 24 kg is far above the 97th centile.

CASE 2. II 1

This, the first born male child of normal parents, died suddenly aged 3 weeks. Necropsy showed pulmonary valve stenosis, left ventricular subendocardial fibrosis, a patent ductus arteriosus, and anomalous systemic venous drainage.

CASE 2. II 2

The sister of case 2.II 1, she developed cardiac failure at 3 weeks of age. Cardiac catheterisation showed an enlarged heart with raised pulmonary artery pressure and end-diastolic pressures in both ventricles. There was a left to right shunt through a patent foramen ovale. The cardiac failure responded to medical therapy. As she was ill in early infancy, little visual responsiveness was expected. Nystagmus was noted at 4½ months, she was photophobic, and poked or rubbed her eyes. At 8 years her binocular acuity was 3/60 and N18, and she had poor colour vision. By 14 years she has no perception of light, a marked ptosis with poor lid creases, and nystagmus. The pupils are mid-dilated and do not respond to light. There is a posterior lens opacity. Retinoscopy measurements are: right +5·00/+1·00 at 90° and left +5·50/+1·00 at 90°. There are pale optic discs, narrow retinal arterioles, thin retinal pigment epithelium and some pigment clumping.

No ERGs or visually evoked responses (VERs) were detectable. The visual handicap limits her full effort potential, but there is no evidence of cardiac failure. The electrocardiogram shows sinus rhythm with a mild intraventricular conduction delay. Cross-sectional echocardiography shows only that the left ventricle is dilated, with the shortening fraction being only 18%. Her height is 100·8 cm (on the 3rd centile) and weight 23·5 kg (above the 90th centile).

CASE 2. II 3

The brother of cases 2.II 1 and 2.II 2, he presented at aged 6 weeks with cardiac failure which responded to therapy. Nystagmus was noted at 4 months, but he had smiled to a face by 2 months of age, and a visual defect was only suspected at 1 year. He was photophobic, and at 22 months paradoxical pupil responses were noted. The ERG from each eye was of small amplitude, and the flash VERs were markedly attenuated and degraded.

At 8 years of age his corrected visual acuity is 3/60 right, 4/60 left, and N14 at 4 inches (10 cm). He had defective colour vision, identifying only the control plate of the Ishihara series. The optic discs are pale, with narrow retinal arterioles but no pigment clumping. Retinoscopy is +7·00 dioptres sphere right, +7·50 dioptres sphere left. He is well without any medication, and in sinus rhythm with mild ST wave changes anteriorly on the electrocardiogram. Cross-sectional echocardiography shows only that the left ventricle is dilated, the shortening fraction being

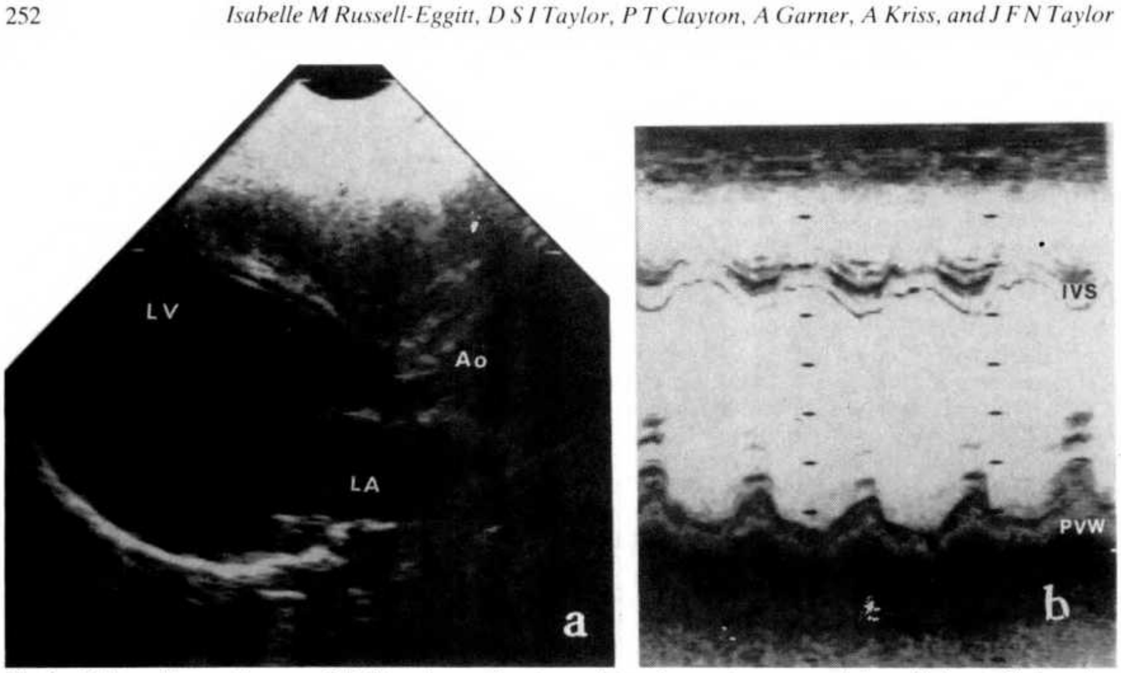

Fig. 2 *Echocardiogram from case 2.II 3 (markers at 1 cm intervals).* a: *Long axis parasternal view of left ventricle in early systole. The ventricle is very dilated and the wall is not thickened.* b: *m Mode scan demonstrates an end diastolic dimension (EDD) of 5·4 cm, and an end systolic dimension (ESD) of 3·6 cm (normal range for BSA EDD: 2·7–4·9 cm, ESD 1·7–3·2 cm). LV=left ventricle. LA=left atrium. Ao=aorta. IVS=interventricular septum. PVW=posterior ventricular wall.*

26%. His height is 123 cm (below the 50th centile) and weight 40 kg (above the 97th centile).

CASE 3. II 1

This, the first born female child of normal parents, died at age 9 weeks. The original diagnosis was renal failure, but death may have been due to cardiac failure. Her eyes had made 'fluttering' movements and she disliked sunlight.

CASE 3. II 3

The brother of case 3.II 1, he collapsed at age 4 months owing to cardiac failure secondary to cardiomyopathy. This responded to medical treatment. At 6 months nystagmus and photophobia were noted. At 3½ years he seemed to see well but sat close to the television. Paradoxical pupil responses were noted on clinical examination. The retinal arterioles were narrow and there was a sheen round the fovea. The flash ERG was undetectable, and the flash VER was greatly reduced in amplitude. At 5 years his unaided visual acuity was 2/36 for each eye and N18. He could name primary colours correctly. There was +8·00 dioptres of hypermetropia in each eye. The retinal arterioles were narrow, but there was no abnormal retinal pigmentation. His visual fields appeared constricted. He attends a school for the handicapped; his IQ is 79 as assessed on the British Ability Scale, WPPSI, and Merrill-Palmer. At aged 5 years there is no evidence of cardiac failure. His electrocardiogram shows a low-voltage trace for a child but is otherwise normal. His cross-sectional echocardiogram shows only that the left ventricle is at the upper limit of normal dimensions, with a shortening fraction of 35% and a slight increase in ventricular wall thickness. His height is 100·8 cm (on the 3rd centile) and weight 23·5 kg (above the 90th centile).

CASE 3. II 4

The sister of cases 3.II 1 and 3.II 3, she was also photophobic and had nystagmus and poor vision; she died from cardiac failure at 2 years. Post-mortem examination showed abnormalities throughout the skeletal muscle, with considerable variation in fibre size. The heart muscle showed swollen hypertrophic nuclei, with fibre variation and large eosinophilic fibres consistent with a dystrophy. The brain showed some neuronal cortical degeneration. Retinal histology failed to show a differentiated macular region and poor definition of the outer plexiform layer, and the photoreceptor outer segments were slightly stunted. The retinal pigment epithelium particularly near the posterior pole and in the peripapillary region was distinctly hypomelanised.

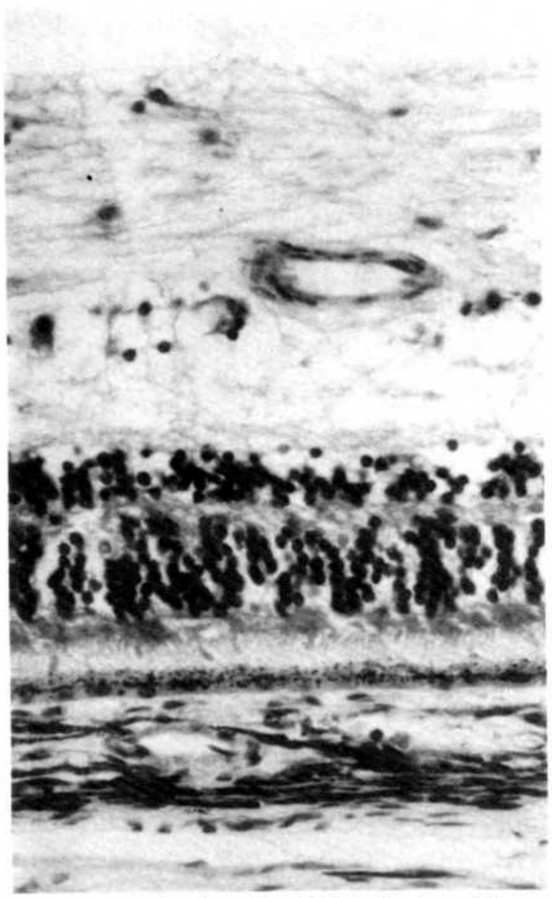

Fig. 3 *Ocular histology of case 3.II 4. Histology of the peripapillary retina shows a prominent nerve fibre layer and a well-defined inner plexiform layer. The outer plexiform layer, however, is almost non-existent. Photoreceptor outer segments, including both rods and cones, are seen, though their development appears to be stunted. The melanin content of the pigment epithelium is markedly reduced. Haematoxylin and eosin, ×340.*

CASE 4.II 1

A male child was stillborn at 6 months gestation, with birth weight 625 g. The mother was suffering from pre-eclampsia.

CASE 4. II 2

The birth of this girl was induced at 35 weeks gestation because of maternal hypertension. Her birth weight was 2443 g and development was normal until 6 months of age, when nystagmus and photophobia were noted. She learned to read large print books, but by 9 years of age she had lost perception of light. At 10 years the ERG was absent. There were roving eye movements, 5 dioptres of hypermetropia, pale optic discs, and attenuated retinal vessels, with perifoveal and equatorial pigmentation. At age 28 years there are posterior lens opacities. The fundus now has diffuse clumps of pigmentation and pigment epithelial atrophy. There have been no episodes of heart failure. Cardiovascular clinical examination, ECG, and echocardiogram gave normal results. Her weight is 70 kg and height 147·5 cm (her mother is 152 cm and father 178 cm).

CASE 4.II 3

This was the brother of 4.II 2. His birth was induced because of maternal hypertension at 32 weeks, and he weighed 1363 g. At 2 months he was floppy and had poor vision and by 4 months had difficulty in breathing owing to myocarditis or endocardial fibroelastosis. He had several episodes of cardiac failure, only partially controlled with digitalis. At 10 years he was photophobic, with visual acuities of 3/60 right, 2/60 left, and N18 held very close. There were pendular nystagmus, a sluggish pupil response, and normal optic discs but narrowed retinal vessels. There was no recordable ERG. His vision was no perception of light by his teens, and he died of heart failure at 19 years. He was never obese despite being wheelchair bound from 14 years.

FURTHER INVESTIGATIONS

Other tests performed on cases 2.II 2, 2.II 3, and 3.II 3 that failed to show any significant abnormality were: full blood profile (no vacuolated lymphocytes were seen), plasma urea, electrolytes and liver function tests, plasma bile acids and very long chain fatty acids, serum phytanic acid, and chromosome analysis (including G banding).

Discussion

With the passage of time the disease that Leber initially described has become more complex as more of these rare cases are grouped and documented. It appears that within the broad group of LCA lie various subgroups. Some are clearly defined: those with mental retardation, with renal disease, which may overlap with Senior's syndrome, with a saccade defect, and with a variety of fundus defects. It is not yet clear whether these cases are genetically distinct or what is their visual prognosis.

The syndrome that we describe is probably a genetically distinct subset of Leber's congenital amaurosis featuring a profound and progressive visual defect with a severely reduced electroretinogram, and cardiac failure with reduction in left ventricular function appearing acutely in infancy. Although the visual prognosis is very poor, if the patient survives the acute cardiac decompensation the prognosis for life appears to be good, though the left ventricle does not recover fully.

The above cases emphasise the need for a general examination in cases of LCA. Case 1.II 2 became severely ill while under investigation for poor vision. The association between LCA and renal abnormalities is already well known, but this important association of cardiac failure with apparently classical ocular features of LCA has not been reported previously. In three cases the visual failure has progressed to no perception of light, which is unusual in LCA.

The surviving children are all obese, but this may reflect reduced exercise owing to their visual handicap. Four are short; three below the 10th centile, one just above the 25th centile. The fifth child (case 1.II 2) is on the 90th centile for height but she comes from a tall family and her weight exceeds the 97th centile. A particular habitus may be part of this condition. The affected individuals, as their parents spontaneously commented when they met, look more similar to each other than to their normal siblings or parents.

Muscle biopsy has not been considered justifiable in most cases, but in the two cases examined at postmortem features of a mitochondrial myopathy were not seen. An enzymatic defect has not as yet been identified. Evidence for a peroxisomal defect was sought by measurements of plasma bile acids, very long chain fatty acids, and phytanic acid. There are few reports of ocular histology in LCA, and we report our cases with the caution in that this may not be typical of classical LCA.

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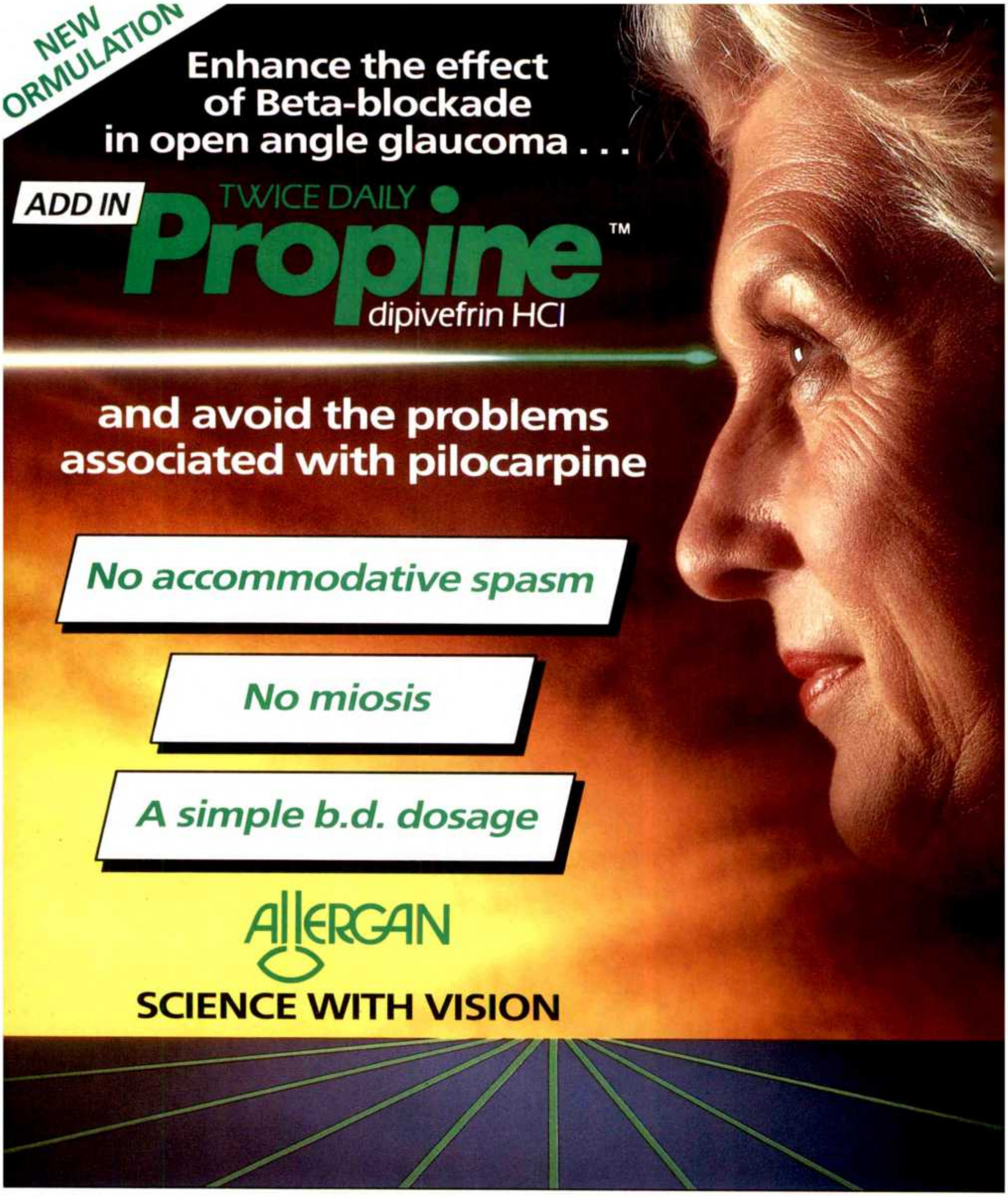

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Does vitreous fluorophotometry reflect severity of early diabetic retinopathy?*

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SUMMARY To determine the relationship between vitreous fluorophotometry (VF) and severity of diabetic retinopathy (DR) 13 patients with mild to moderate background DR starting continuous subcutaneous insulin infusion were followed up serially for 12 months. They were studied by colour stereo retinal photographs, which were assessed by the Wisconsin Grading System, and by VF, which was assessed by the permeability index of the retina for fluorescein. By four months the severity of DR on colour photographs had deteriorated by at least one level in at least one eye in eight patients. In four patients the DR did not deteriorate. Assessment of anatomical abnormalities by severity of DR on colour photographs correlated well with the functional abnormalities of the blood-retinal barrier(s) assessed by VF, especially for the macular field. Comparison of permeability index data in the patients developing preproliferative or proliferative features of DR (group A) with the same data in patients who did not develop such changes (group B) indicated that group A patients had more severe DR than did group B patients at entry. Grading of colour photographs showed a similar trend but with greater overlap. Considerable overlap in fluorescein permeability remained between those subjects with no visible DR and those with microaneurysms with or without haemorrhages and small hard exudates.

Vitreous fluorophotometry (VF) was developed 20 years ago[1] in the expectation that it would enable a functional abnormality to be identified in patients at risk of developing diabetic retinopathy (DR) prior to the appearance of overt structural abnormalities. Early studies[2-5] suggested that this might indeed be the case. However, several groups found considerable overlap between patients with no or minimal retinopathy and the normal range,[6-8] despite the use of standardised equipment (Fluorotron Master, Coherent Radiation, Palo Alto, CA) and rigorous mathematical analysis of the data obtained.[9] Since only small anatomical differences are present between subjects with no DR and those with minimal DR, correlation was then sought between the degree of fluorescein permeability of the blood-retinal barrier(s) measured by VF, and severity of the structural abnormalities through a larger range of patients encompassing mild to moderate background DR. Patients beginning treatment with continuous subcutaneous insulin infusion (CSII) were selected for study, since earlier reports indicated that significant retinal changes might be observed within a few months of starting CSII.[10-12]

Patients and methods

Thirteen consecutive patients attending the Diabetic Retinopathy Clinic, Hammersmith Hospital, who also accepted CSII were included in the study. Patients with ketosis-prone insulin-dependent diabetes of at least five years' duration and with background DR were studied, who were otherwise in good health and normotensive with diastolic blood pressures not exceeding 90 mmHg. They received no treatment other than insulin. The patients were admitted to the Metabolic Unit of the hospital for three to four days for familiarisation with the infusion device and for serial monitoring of capillary blood glucose concentrations (BM 20–800R sticks, Boehringer Mannheim). Before starting CSII all the

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patients were examined by indirect and direct ophthalmoscopy and slit-lamp biomicroscopy to exclude posterior vitreous detachment, and stereo colour photographs of the seven standard fields of the Diabetic Retinopathy Study[13] were taken. Fluorescein angiography and vitreous fluorophotometry were performed at the same time, and blood was taken for estimation of total glycosylated haemoglobin (HbA_1) by gel electrophoresis (Glytrac kits, Corning, Palo Alto, CA). These investigations were repeated after one, four, and 12 months of CSII treatment, and HbA_1 was measured at eight months in addition.

Stereo retinal colour photographs were graded by comparison with the standard photographs of the Diabetic Retinopathy Study Research Group[13] by an observer who was masked as to patient identity and to sequence of the photographs. Levels of severity of DR were assigned according to the criteria of the Wisconsin Study[14] as modified by Canny *et al.*[15] This provided a standardised anatomical assessment of the severity of retinopathy. Briefly, levels of severity corresponded to the following lesions:

Level 10: no retinopathy.

Level 20: microaneurysms only.

Level 30: microaneurysms and at least one of haemorrhages, small hard exudates, venous loops, questionable cotton-wool spots (CWS), questionable intraretinal microvascular abnormalities (IRMA), and questionable venous beading (VB).

Level 40: microaneurysms and at least one of definite CWS, definite IRMA, definite VB, moderate or large hard exudates, or severe haemorrhages.

Level 50: combinations of severe haemorrhages, CWS, IRMA and VB in the four peripheral fields.

Level 60: neovascularisation or fibrous tissue associated with new vessels, or photocoagulation for neovascularisation.

Vitreous fluorophotometry was performed on both eyes by means of the Fluorotron Master (Coherent Radiation, Palo-Alto, Calif) during the one hour after bolus intravenous injection of 14 mg/kg 20% sodium fluorescein angiography. Fluorophotometry data were analysed initially using the optimised protocol supplied by the manufacturer. From the data and from measurement of plasma-free (non-protein bound) fluorescein a permeability index for fluorescein of the blood-retinal barrier(s) of the perimacular retina was derived, as described previously.[16] This provided an assessment of the functional abnormalities due to DR and allowed comparison with the structural abnormalities observed on retinal photographs. Units of permeability index were 10^{-7} $cm.s^{-1}$. The concentration of fluorescein glucuronide[17-19] was considered in concentration equivalents of fluorescein, on the assumption that the transport rates of free fluorescein and free fluorescein monoglucuronide across the blood-retinal barrier(s) were equal.[20 21]

Patients were separated into those who within four months showed deterioration, with the appearance of new preproliferative (CWS or IRMA) or proliferative features (group A), and those who did not deteriorate or in whom change was limited to the appearance of haemorrhage in eyes in which DR was characterised previously by the presence of microaneurysms alone (group B). Severity of retinopathy was compared with the permeability index. The mean of the permeability index for the right and left eye was used for each patient, and values were log-transformed to obtain a normal distribution. Mean values of the log-transformed permeability index for all visits for all patients were then plotted against level of severity of DR. Finally, to determine the relative importance of DR in the macular field alone compared with that of the eye as a whole in leading to elevation of the permeability index, all log-transformed permeability index data were also plotted against level of DR in the macular field (field 2).

Approval for the study was obtained from the Ethics Committee, Hammersmith Hospital, and all patients gave informed consent prior to entry.

Unless stated otherwise, the statistical significance of differences between groups was assessed by Student's paired and unpaired *t* test, as appropriate. The relationship of PI to retinopathy severity was studied by χ^2 and Kruskar-Wallis tests.

Results

Of the 13 subjects only two were female. One of these developed florid neovascularisation at four months and required bilateral panretinal photocoagulation. Two other patients did not complete 12 months of study; one departed permanently from the UK after the four-month assessment, and the other died suddenly of lung carcinoma prior to the four-month assessment. Vitreous fluorophotometry data on the latter patient at one month could not be recovered from a faulty computer disc, and this patient was excluded from the analysis. All other patients completed 12 months of CSII treatment successfully.

PROGRESSION OF DR BY GRADING OF COLOUR PHOTOGRAPHS

Severity of DR at entry was assessed at level 20 in four eyes of two patients, at level 30 in nine eyes of six patients, and at level 40 in the remaining 11 eyes of eight patients. Patients who deteriorated were compared with those whose DR remained at a milder

Table 1 *Severity of retinopathy in patients beginning CSII*

Patient	*Entry*	*Months of study*		
		1	*4*	*12*
*Group A**				
1	7	7	8	8
2	6	7	7	7
3	7	8	11	*
4	6	7	6	7
5	6	7	6	–
6	6	6	7	5
7	5	5	7	
Group B				
8	3	4	3	4
9	5	5	5	6
10	6	5	5	5
11	7	6	7	7
12	3	3	3	3

*Required photocoagulation.
Severity is adapted from the method of Canny *et al.*,[15] keyed to the worse eye. Level 10/10=1, 20/10=2, 20/20=3, 30/20=4, 30/30=5, 40/30=6, 40/40=7, 50/40=8, 50/50=9, 60/50=10, 60/60=11

Table 3 *Permeability index and glycosylated haemoglobin. means (SD)*

Group	*Entry*	*Months of study*		
		1	*4*	*12*
1 log Permeability Index (cm.s⁻¹)				
A	0·75 (0·31)	0·69 (0·40)	0·91 (0·49)	0·67 (0·30)
B	0·35 (0·15)*	0·38 (0·13)	0·37 (0·07)†	0·47 (0·12)
2 Glycosylated haemoglobin (%)				
A	11·2 (2·0)	9·6 (1·3)	8·3 (1·7)‡	9·8 (0·6)
B	10·3 (0·1)	10·0 (1·1)	9·7 (2·6)	9·2 (0·7)

*p<0·05 vs group A log-transformed permeability index at entry
†p<0·05 vs group A log-transformed permeability index at 4 months.
‡p<0·05 vs group A HbA_1 at entry.

level by the step-wise system of grading severity keyed to the worse eye[15] (Table 1). By four months a total of eight patients had deteriorated by at least one level in at least one eye, and, of these, seven had developed new CWS, IRMA, or neovascularisation. In the remaining patient, deterioration was restricted to the appearance of haemorrhage in an eye in which DR was previously at level 20. This patient was considered together with those whose DR did not change by four months. Fluorescein angiograms in general showed qualitative deterioration in parallel with changes on colour photographs.

Table 2 *Mean retinal permeability index by vitreous fluorophotometry*

Patient	*Entry*	*Months of study*		
		1	*4*	*12*
Group A				
1	10·1	14·4	13·7	8·25
2	6·44	3·01	8.87	10·7
3	19·9	20·7	65·8	–
4	2·66	3·01	2·23	3·96
5	3·91	1·92	6·18	1·90
6	3·95	2·47	2·69	–
7	3·11	5·37	8·05	3·41
Mean (SD):	7·15 (6·18)	7·27 (7·33)	15·36 (22·75)	5·64 (3·68)
Group B				
8	1·37	1·97	2·15	2·71
9	2·21	1·75	2·07	2·27
10	2·14	3·24	3·10	2·77
11	3·73	3·34	2·42	4·64
12	3·11	5·37	8·05	3·41
Mean (SD)	2·34 (0·86)	2·48 (0·75)	2·37 (0·43)	3·05 (0·92)

Individual values (10^{-7} cm s^{-1}) are mean of the right and left eye on each occasion (except patient 8 (entry) and patient 12 (entry and 1 month), which are for the right eye only).

RETINAL PERMEABILITY TO FLUORESCEIN BY VITREOUS FLUOROPHOTOMETRY

Table 2 shows the mean permeability index for right and left eyes in each patient (except subject 8 – initial visit – and subject 12 – initial and one-month visits when data for the right eye only were obtained). Table 3 shows the mean permeability index and HbA_1 data in group A (patients who deteriorated on colour photographs by four months) and in group B (non-deteriorators). The mean of the log-transformed permeability indices at entry was significantly higher in group A than in group B ($p<0·05$), with only one patient in group A falling into the normal range and one in group B with a value above the upper limit of normal. Patients in group A could not be distinguished from those in group B by consideration of the vitreous fluorescein concentrations 3 mm anterior to the retina, as obtained from the optimised protocol-adjusted measurement scans at 1 h.[22] As shown in Table 1, patients who deteriorated (group A) were noted to have slightly more severe DR at entry (steps 5, 6, 6, 6, 6, 7, 7) than patients in group B (steps 3, 3, 5, 6, 7), but this difference did not reach statistical significance (Mann-Whitney test statistic 25·5, p=0·17). Patients in group A also achieved a significant fall in HbA_1 by four months, whereas HbA_1 did not change significantly over the course of 12 months.

RELATIONSHIP BETWEEN PERMEABILITY INDEX AND RETINOPATHY LEVEL

Fig. 1 shows the relationship between the logarithm

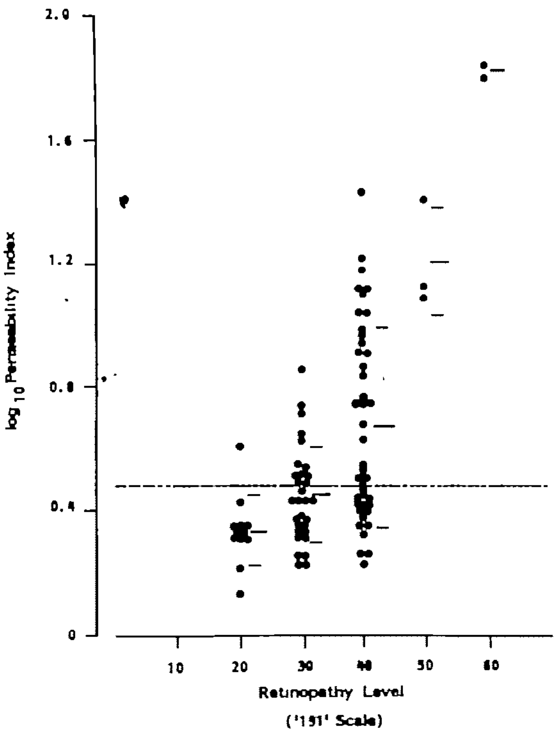

Fig. 1 *Relationship between level of severity of retinopathy for individual eyes and the logarithm of the permeability index determined by vitreous fluorophotometry The interrupted line indicates mean +1 SD determined previously in normal subjects.*[14]

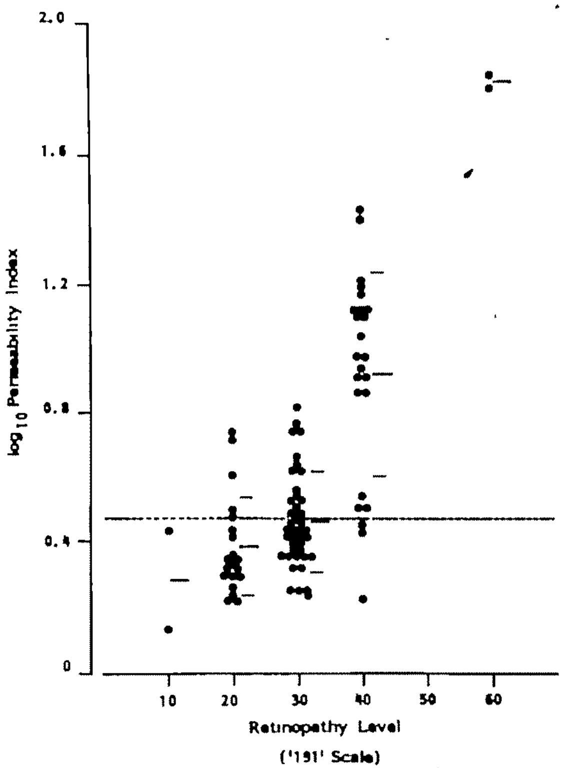

Fig. 2 *Relationship between level of severity of retinopathy for the macular field (field 2) alone, and the logarithm of the permeability index determined by vitreous fluorophotometry. The interrupted line indicates mean +1 SD determined previously in normal subjects.*[14]

of the permeability index and retinopathy level for all observations throughout the 12 months of study. The mean +1 SD of permeability index in normal subjects determined previously[14] is shown as the interrupted line, and demonstrates clearly the large overlap between values obtained in eyes with mild DR and the normal range. The correlation of permeability index or its logarithm with level of severity of DR was highly significant statistically (Kruskal-Wallis statistic=23·2, $p<0·0001$ by χ^2, values for levels 40, 50, and 60 being combined to avoid cells with small numbers of observations). Correlations of the severity of DR in the macular field (field 2) with permeability index was then sought. DR of level 50 is defined as a combination of preproliferative factors in four peripheral fields (superior and inferior temporal and nasal fields); hence this level did not apply. Results are shown in Fig. 2, and even better correlation was obtained statistically between the parameters (Kruskal-Wallis statistic=38·9, $p<0·0001$, by χ^2, values for levels 10 and 20 and levels 40 and 60 being combined to avoid cells with small numbers of observations).

Discussion

This study confirms the results in a previous communication from this department in another group of patients, namely, that in those with no or minimal DR (levels 10, 20) the use of VF does not always demonstrate a difference from normal persons.[9] In eyes with more severe DR (levels 30–60) the permeability index rose progressively, but some overlap remained between successive groups of patients. However, a good correlation between anatomical lesions (photographic severity) and the degree of the functional defect in the blood-retinal barrier(s) (measured by VF) existed at these more severe levels of DR.

A recent report from Chicago demonstrated a close relationship between the extent of disruption of the blood-retinal barrier of the perimacular retina, as measured by a posterior vitreous fluorophotometry penetration ratio, and visual acuity in patients with diabetic macular oedema.[23] The amount of leakage also correlated well with the area of retinal thickening in the macular field as judged by grading of stereo colour retinal photographs. The results of the present study in patients with no visual loss due to macular oedema (except for patient 6 at four months) indicate a better correlation between the severity of DR in the macular field and the permeability index than between the severity of DR for the eye as a whole and the permeability index, and support the findings of Smith *et al.*[23] From the results of these studies it appears that vitreous fluorophotometry with Fluorotron Master will be of value as an additional investigation in diseases of the macula and perimacular retina rather than in conditions affecting the peripheral retina. It also suggests that one hour complete, even distribution of fluorescein may not have been obtained.

The exact pathogenesis of the deterioration of DR in patients beginning CSII remains to be determined. A variety of lesions including new vessels have been reported,[24] of which the most striking feature is the appearance of multiple CWS.[11,25] It has been suggested[11,26] that the major causal factor was the rapid lowering of blood glucose concentrations (or changes of associated parameters) resulting indirectly in reduced retinal perfusion, leading to nerve fibre layer infarction and to the appearance of CWS. It is possible that other factors may contribute to the deterioration in these patients. Alternatively, ischaemia may be manifested in the appearance of IRMA and haemorrhages. In this study patients who deteriorated (group A) had a reduction in HbA_1 by four months, whereas this was not observed in group B. It is therefore possible that, in this small series also, reduced blood glucose concentrations contributed to the deterioration of DR in group A.

In summary, the data presented suggest that subjects with disruption of the blood-retinal barrier(s), manifested as increased permeability of the perimacular retina to fluorescein, may be at higher risk of deterioration of DR after the institution of CSII, whereas those with milder DR may avoid such deterioration. Furthermore, the pooled data suggest a good correlation between the degree of functional abnormality measured by VF and the severity of structural lesions assessed by a standardised grading technique. The patient who required photocoagulation reconfirmed previous reports that institution of CSII with improved glycaemic control does not prevent the development of neovascularisation.

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The EEC syndrome and its ocular manifestations

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SUMMARY The EEC syndrome (ectrodactyly or lobster-claw deformity, ectodermal dysplasia, and cleft lip and palate) is a rare disorder with autosomal dominant inheritance, variable expression, and in some families lack of penetrance. We present the findings in five cases with emphasis on the ocular findings. Lacrimal surgery was performed on three patients with good results in each case. We also report the occurrence of spontaneous corneal perforation in two cases, a complication not previously recognised. The ophthalmic care of these patients must be pursued long-term, as progressive visual impairment may be the most disabling feature of the syndrome.

The EEC syndrome, and acronym coined by Rudiger *et al* in 1970,[1] was first recognised as a distinct clinical entity by Cockayne.[2] He drew attention to the dacryocystitis which commonly afflicts these patients, and found that it was associated with 'atresia of the lacrimal ducts.' Since that description in 1936, several other reports have appeared in the ophthalmic literature[3-6] detailing the ocular findings in the syndrome. Five cases in three families have presented to the Lacrimal Clinic at Moorfields Eye Hospital between 1981 and 1987 and three have undergone lacrimal surgery.

We present the clinical details of each of these five patients, three of whom are from one family, a mother and two daughters.

Case reports

CASE 1

This girl is an older sister of case 2 and the daughter of case 3. She is the third of four children, an older brother and sister being unaffected. Her parents are unrelated and of Sikh Indian origin.

Both eyes had watered from birth, with intermittent mucopurulent discharge. She had been born after a normal pregnancy with bilateral cleft lip and palate which were surgically repaired at the age of 6 months. Her right hand showed ectrodactyly and a surgical procedure was performed at 6 years to provide a more functional hand. Both feet had syndactyly. Her hair was coarse and dry and her skin subject to eczema. She had a bilateral conductive hearing loss and wore hearing aids. There was bilateral malar hypoplasia and small malformed teeth.

We first saw her at the age of 11 years. Visual acuity was 6/6 right and 6/5 left. Her lids were thickened by an eczematoid skin change and were cracked and scaling. There was a moderate watery discharge from each eye. All four lacrimal puncta were occluded by a thin membrane, but their positions were normal and easily discernible. Slit-lamp examination was hampered by severe photophobia, but both corneas appeared normal, and the irides were brown without any transillumination defects. The rest of the ocular examination gave normal findings.

Each lacrimal system was explored under general anaesthesia on separate occasions, and the findings were similar. The thin membranes occluding the puncta were easily perforated by a punctum dilator, but there was no true ampulla. Probes passed easily into the lacrimal sac, but the lid margins medial to the puncta were thinned, with the probes seen easily through the overlying epithelium. When exposed, the lacrimal sac was found to be grossly enlarged, thin walled, and filled with mucus. There was no membranous or bony nasolacrimal duct. A formal dacryocystorhinostomy (DCR) was performed on each side with intubation of the canaliculi. The tubes cheese wired through the lid margins for 2-3 mm and were removed after one month. The patient is free of epiphora.

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CASE 2

This girl is the youngest of four children and the sister of case 1. She was brought to the Lacrimal Clinic at the age of 3½ years with a history of bilateral epiphora from birth. She had been born after a normal pregnancy with bilateral cleft lip and palate. There was ectrodactyly of both hands and the left foot, with mild syndactyly of the right foot. At nine months the cleft lip and palate were repaired, and at 4½ years the more severely affected left hand was modified to provide a more functional grip.

The child's skin was noticeably fairer than her parents' and her hair was coarse and dry, with patchy alopecia. There was malar and mandibular hypoplasia, but her first dentition appeared normal other than being carious. She wore a hearing aid on the right for a conductive hearing loss.

The right lacrimal system had been probed and intubated at another hospital at nine months, and the tube remained in situ for three weeks. Watering persisted after its removal. When she was first seen in the Lacrimal Clinic aged 3½ visual acuities were normal. The right upper and lower puncta appeared slit-like. The left puncta and lids were normal. There were bilateral mucocoeles. The rest of the ocular examination gave normal results.

Right and then left DCRs were performed three months apart. On the right there was a large mucocoele, with an obstructed nasolacrimal duct. The bony nasolacrimal canal was, however, present. On the left the lacrimal sac was again dilated, but there was no membranous or bony nasolacrimal canal. Both DCRs were successful, and the child is free of watering.

CASE 3

The mother of the two girls above (cases 1 and 2) had only mild features of the syndrome. Her left hand showed polydactyly with a rudimentary digit attached to the radial side of the thumb and syndactyly of both feet. There was no lip or palate abnormality, and ocular examination gave normal findings apart from some trichiasis of the medial third of each lower lid and slight retroplacement of the lower puncta behind the lid margin. Skin, hair, and teeth were of normal appearance. There were no further affected family members.

CASE 4

This boy was first seen by us at the age of 13 with a spontaneous corneal perforation. He had been born with multiple abnormalities including a left sided cleft lip and palate, ectrodactyly of both hands, and syndactyly of the right foot. He had required bilateral reimplantation of the ureters for vesicoureteric reflux. His skin had always been dry. There had been recurrent bouts of sticky discharge from both eyes since birth, but there was no watering between these episodes. The only positive family history was a 'crippled' maternal grandfather, but no details were available. His parents and one sibling, a brother, are unaffected.

Two months before presentation to Moorfields he had again developed a discharge from the left eye. This was treated with topical gentamicin, tetracycline, and weak steroid drops, but the symptoms were slow to resolve. On the day before admission he felt a sudden 'flash' in the eye followed by watering and blurred vision. Visual acuity was 6/4 right and 6/36 left. The left cornea had an area of central thinning, with a small perforation below the visual axis and a shallowed anterior chamber. The perforation was sealed by a knuckle of iris (Fig 1). Both corneas also showed old peripheral stromal infiltrates and scars. He had normal brown irides. The lids showed mild blepharitis. Both upper puncta were absent as was the right lower punctum. The left lower puntum was normal, but there was a lacrimal fistula opening on to the skin several millimetres below the medial canthus, and pus was easily expressible from it on massaging the lacrimal sac.

The corneal perforation was managed conservatively with the fitting of a soft silicone lens. The anterior chamber reformed, and the perforation healed. Vision recovered to 6/9, and the cornea was left with a small stromal scar just below the visual axis and some peripheral superficial stromal vascularisation and infiltrates.

A dacryocystogram was performed and showed a

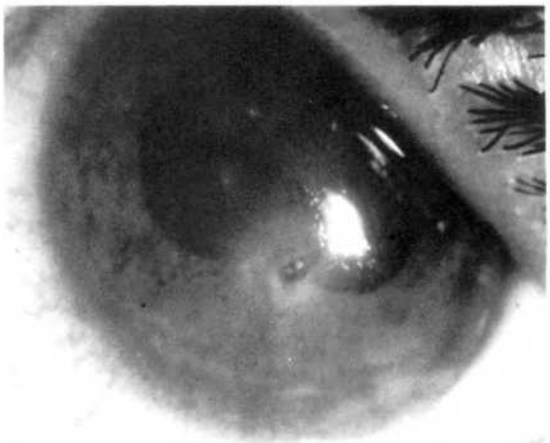

Fig. 1 Case 4. Spontaneous perforation of the left cornea. There is an area of central thinning and a small perforation plugged by iris. A soft silicon contact lens is in situ. Vision recovered to 6/9.

mucocoele with a diverticulum. Five months later the left lacrimal system was surgically explored. The fistula originated from the common canaliculus (the commonest site for the origin of congenital fistulas[7]). It was excised and a formal DCR completed. No upper canaliculus was found, and there was no bony nasolacrimal canal. The patient has been free of discharge up to five years later. It was decided not to operate on the right lacrimal system as there was no watering and no evidence of a mucocoele.

CASE 5

We first saw this young woman at the age of 23. She had been born with ectrodactyly of all four extremities (Figs 2 and 3) and ectodermal dysplasia manifest as dry skin and coarse dry hair. She had required multiple dental procedures for partial anodontia and hypodontia. Her father suffered from the same condition, but there was no other positive family history, her two siblings being unaffected. Unfortunately the father refused to be examined, but he was reported as having the same skin, hair, dental, and limb anomalies. Neither he nor his daughter had abnormalities of the lip or palate.

Both eyes watered from birth, and she had an unsuccessful right DCR in childhood. In more recent years she felt her eyes were dry, and she had used artificial tears with some relief. At the age of 21 her right cornea had spontaneously perforated without any antecedent history of infection. It had healed with the aid of a soft contact lens, and no surgery was required. Early in 1987 she had developed acute right dacryocystitis requiring systemic antibiotics.

When seen by us in December 1987 the vision was 6/18 in the previously perforated right eye and 6/12 in the left. There was trichiasis of the medial third of the lower eyelids. The right upper punctum was absent and the lower was occluded by a thin membrane with only 2 mm of canaliculus on probing beyond this. There was no clinical evidence of the mucocoele and no patency on attempted syringing through the lower punctum. The puncta and canaliculi were normal on the left with patency to syringing. There was a poor tear film on each side. The right cornea showed extensive superficial stromal vascularisation with central thinning. On the left there was some pannus superiorly. The remainder of the ocular examination was normal. The irides were blue and the hair pale brown.

It was elected not to perform lacrimal drainage surgery on the right unless she developed a further attack of dacryocystitis.

Discussion

From the five cases presented it is apparent that the EEC syndrome has a variable expression. In naming this the EEC syndrome, Rudiger *et al.*[1] drew attention to the three features of the condition, namely ectrodactyly, ectodermal dysplasia, and cleft lip and palate. Dacryocystitis secondary to congenital lacrimal duct anomalies was noted by Cockayne in the first published report of the syndrome.[2] Other patients reported in the ophthalmic and general literature[3-6 8-10] have had varying combinations of blepharitis, conjunctivitis, corneal scarring, and pannus with photophobia, and poor lacrimal and meibomian secretion. Blue irides and albinoid features are said to be common, as is entropion with trichiasis and in some cases madarosis. Most of these affected structures are ectodermally derived, and it is not surprising to see such features in a condition with widespread ectodermal dysplasia manifest elsewhere as skin, hair, nail, and teeth changes. The lacrimal drainage apparatus is also derived from surface ectoderm and commonly affected. Despite its ectodermal origin, the crystalline lens has not been found to be abnormal.

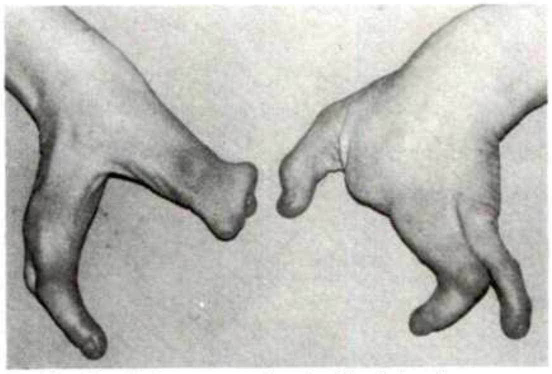
Fig. 2 *Case 5. Severe ectrodactyly of both hands.*

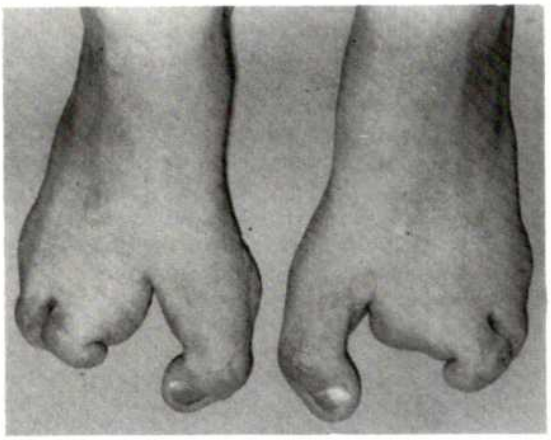
Fig. 3 *Case 5. Ectrodactyly of the feet.*

That two of our patients developed spontaneous corneal perforations seems to be more than coincidence There are many reasons for patients such as these to develop such a complication: the cornea is partially derived from ectoderm, there are tear film and lid abnormalities, there may be trichiasis and an obstructed lacrimal drainage apparatus harbouring potentially pathogenic organisms. One of our patients had been on weak steroid drops, and this may have contributed to the development of the perforation. To the best of our knowledge, however, these are the first reports of this complication in the EEC syndrome. Both responded to conservative treatment with bandage lenses, and good visual acuity was preserved.

The EEC syndrome has been found in association with conductive hearing loss.[11] Our first two cases both had hearing defects. Robinson *et al.* [11] found a congenital absence of the stapes and part of the incus in one of three members of a family whose affected members had a conductive hearing loss in addition to the other features of the syndrome. Urinary tract anomalies as exemplified by case 4 have also been observed by others,[12] and the letters UT (urinary tract) have been appended to EEC to describe the syndrome in such individuals. Rare cases of ectrodactyly and ectodermal dysplasia have also been seen in association with a retinal macular dystrophy and dubbed the EEM syndrome.[13,14] In addition a syndrome of ankyloblepharon, ectodermal defects, and cleft lip and palate (the AEC syndrome) has been described in association with lacrimal duct atresia.[15]

The autosomal dominant inheritance in some families of atresia of the lacrimal canaliculi is well known. Obstruction of the nasolacrimal duct in association with cleft lip and palate is often observed. We have also seen a family with ectodermal dysplasia whose affected members had absent lacrimal puncta. However, in our experience the patients with the EEC syndrome form the largest group, showing an association between limb deformities and lacrimal drainage anomalies. These anomalies are quite variable, however, and are not unique to the EEC syndrome.

Cleft lip and palate are usually repaired early in life, and the patients appear to adapt well to the limb deformities of the EEC syndrome. However, the ocular complications may be progressive and threaten sight. It is therefore important that these patients be under long-term ophthalmic supervision to try to prevent the sight threatening corneal complications and to treat a corneal perforation which threatens the whole eye.

Lacrimal drainage surgery also forms an important part of the management of these rare patients. Obstructed lacrimal canaliculi or nasolacrimal ducts are not in themselves indications for surgery. Tearing seems often to be absent in these patients despite the obstructed outlet and is probably secondary to lacrimal gland dysfunction. In a patient with a dry eye and obstructed nasolacrimal ducts with mucocoele formation and sticky discharge, or frank dacryocystitis, surgery may be required. We operated successfully on three cases and experienced no particular technical difficulties. The only complication was cheese-wiring of the lid margins from the tubes inserted in case 1. This was abetted by the abnormally thin lid margins overlying the canaliculi in this child. We have not found it necessary to resort to dacryocystectomy or Lester Jones bypass tubes as reported in some cases.[4,5]

We thank Mr Roger Buckley for allowing us to include his case, and all the other ophthalmologists who continue to support the Lacrimal Clinic at Moorfields by referring their patients

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Visual evoked potentials in dissociated vertical deviation: a reappraisal

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SUMMARY Pattern reversal and flash evoked potentials were recorded in 13 children with dissociated vertical deviation (DVD). No electrophysiological evidence was found to support the notion that patients with DVD have an anomalous (albinoid) projection of visual fibres originating from the temporal retina of each eye. However, DVD patients had significantly smaller monocular and binocular pattern evoked responses than age matched controls. Explanations are given for this finding and for the occipital VEP asymmetries reported by other workers.

Dissociated vertical deviation (DVD) is an unexplained oculomotor anomaly which becomes evident when the optical input to one eye is occluded or severely degraded. The visually debased eye elevates with extorsion, and latent nystagmus, another commonly associated feature, appears in both eyes. The nystagmus is of the jerk type, with a slow phase towards the covered eye followed by a faster temporally directed jerk. DVD is usually found in patients who had esotropia in infancy, though the condition may not be clinically apparent until a few years after birth.

Fitzgerald and Billson[1] presented pattern evoked potential data which supported their hypothesis that patients with DVD have an anomalous projection in which a significant proportion of fibres originating from the temporal retina cross at the chiasm, together with nasal retinal fibres. This abnormal pattern in projection is similar to that reported to occur in albinos.[2-4]

We have recorded both pattern and flash evoked potentials in young patients with DVD and did not find evidence to support Fitzgerald and Billson's hypothesis. However, we found that pattern reversal responses of DVD patients are not altogether normal, and we suggest reasons for this and for the VEP anomalies reported by Fitzgerald and Billson.[1]

Material and methods

Checkerboard reversal and flash evoked potentials were recorded in 13 patients showing dissociated vertical deviation. Six were male and seven female. The mean age of the group was 8·2 years (SD 4·2, range 3–16 years).

All except one patient had developed esotropia within the first few weeks of birth and had had early surgery. In one patient the squint developed at 1 year of age, and although this patient had DVD and latent nystagmus like the other 12 there was no horizontal component to the deviation, and surgery was not required. All patients had had ophthalmological assessment and orthoptic treatment for a number of years prior to the visual evoked potential (VEP) recordings

Three silver/silver chloride electroencephalograph (EEG) electrodes were applied to the posterior scalp with pyroxylin (Collodion). One electrode was sited in the midline above the inion at a distance of 10% (approximately 4 cm) of the nasion to inion separation. The other two were placed 20% (approximately 4 cm) of the left mastoid to right mastoid distance on either side of the midline electrode. The three occipital electrodes were referred to a common reference, 12 cm above the nasion (Fz, 10–20 system).

The patients sat 1 metre from a 26-inch (66 cm) Sony TV and viewed 50-minute black and white checks of 90% contrast in a full field subtending 28° horizontally and 21° vertically. A small, half degree fixation dot was placed at the centre of the screen.

The checkerboard reversal rate was 3 per second, and responses to full-field and half-field stimulation were recorded. Flash stimulation was also performed with a Devices photic stimulator.

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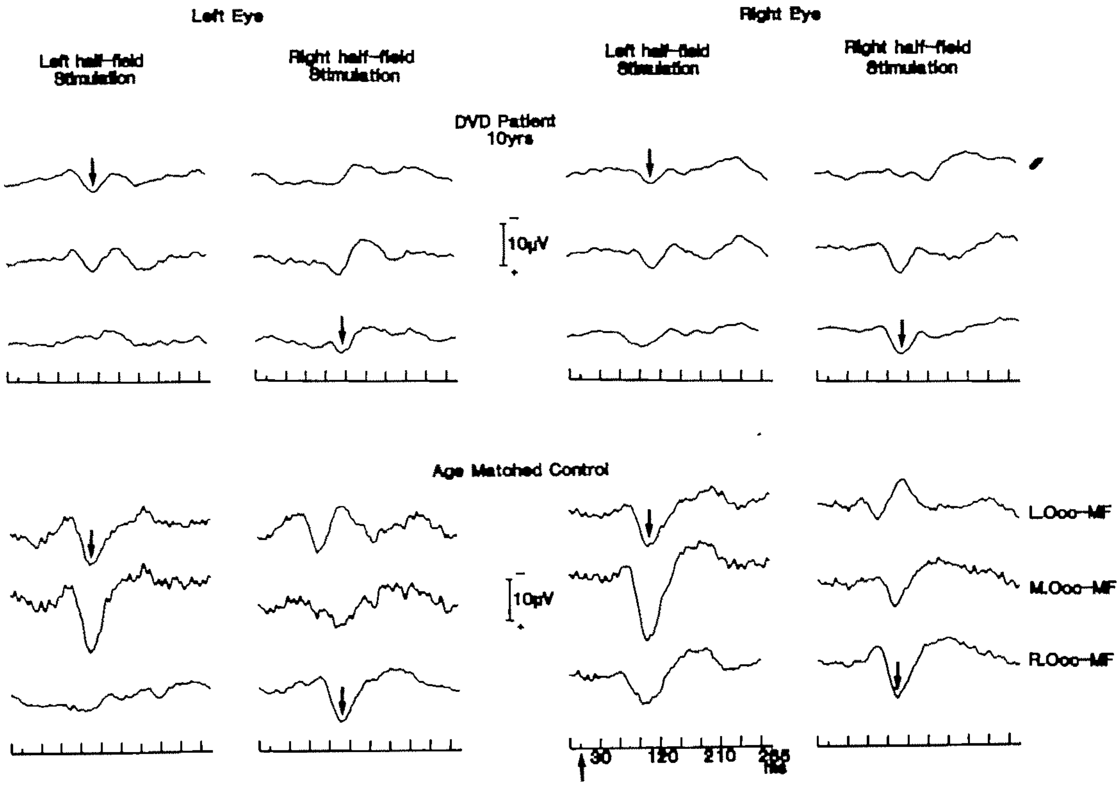

Fig. 1 *Left and right half-field responses from each eye in a DVD patient (upper traces) and an age matched control (lower traces). Note the P100 component (arrows) is seen mainly in the midline and side of scalp ipsilateral to the stimulus field.*

The recording amplifier bandpass was set between 3 and 250 Hz (−3 dB points). The average analysis time was 300 ms, which included a 15-ms prestimulus interval, and 128 trials were averaged with a Medelec Sensor.

Responses from the DVD patients were compared with those of 13 age matched controls (mean 8·3 years, SD 3·4, range 4–15 yr).

Results

There was no consistent nasal/temporal differences in the amplitude of pattern reversal responses to half-field stimulation between patients with DVD and aged matched controls. In both groups the main positive component (P100) elicited by a wide half-field stimulus (0–14° radius) of 50-minute checks, was

Table 1 *Means and standard deviations (in parentheses) of the amplitude of the pattern reversal P100 following full-field and half-field stimulation*

Stimulus	*DVD patients*		*Matched controls*		*Significance level*
	Mean	*(SD)*	*Mean*	*(SD)*	
Binocular full-field	18 1	(7·1)	26·5	(9·8)	<0·05
Left eye full-field	6·2	(2·8)	17·8	(6 7)	<0·01
Right eye full-field	7·2	(4·4)	17·8	(4·9)	<0·01
Left eye left half-field	5 4	(2·3)	9·2	(2·5)	<0·01
right half-field	3·8	(2·2)	9·4	(3·6)	<0 01
Right eye left half-field	4·2	(2 4)	9·5	(2·4)	<0·01
right half-field	5·9	(3·7)	8·9	(2·5)	<0·05

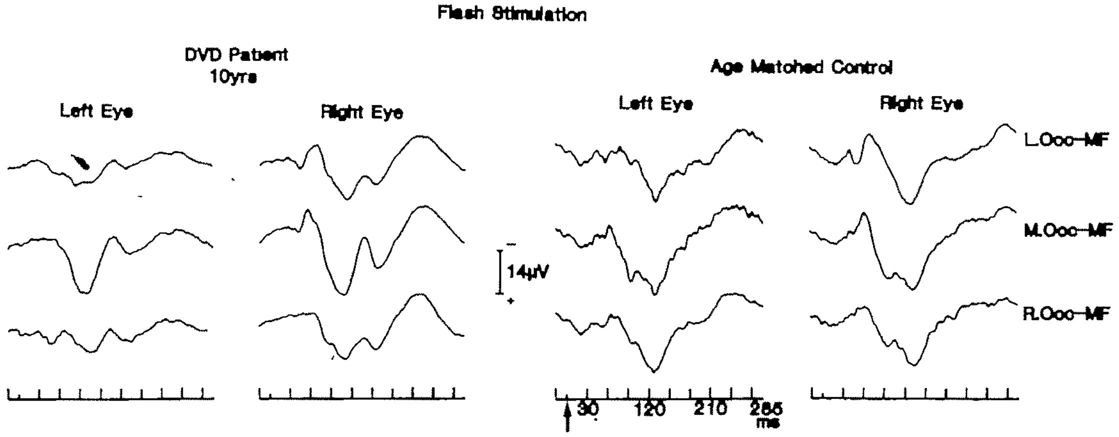

Fig. 2 *VEPs following monocular flash stimulation of each eye. Both the DVD patient (on the left) and the age matched control (on the right) have symmetrically distributed occipital responses.*

recorded in the midline to varying extents, and regularly on the side of scalp ipsilateral to the presented field (Fig. 1). Over the contralateral scalp a positive-negative-positive complex (negativity at around 100 ms) was often evident, though its size varied considerably between individuals and, indeed, in the same individual for left and right half-field stimulation.

Table 1 includes the P100 amplitude values measured at the occipital location ipsilateral to the stimulus half-field. Independent t tests gave no significant differences when comparing left and right half-fields of the same eye or the homonymous half-field of each eye.

Fig. 2 shows the flash VEPs from a DVD patient (on the left) and a match control (on the right) for left and right stimulation. Both patient and control had symmetrical occipital distributions for the flash VEP. There were no significant group differences in the mean amplitudes of the midline main positivity for the flash response between the DVD patient group (left eye 19·5 µV, SD 10·5; right eye 23 µV, SD 6·5) and matched controls (left eye 21·8 µV, SD 6·5; right eye 20·1 µV, SD 7·9). There were also no significant differences when comparing the left against the right sided channel for stimulation of each eye, nor for comparison of each eye's response at the same lateral electrode.

No significant latency differences were found between the patient and control groups for either pattern stimulation (Table 2), or flash stimulation.

Thus DVD patients did not differ from matched controls when the occipital distribution was compared either with half-field pattern stimulation or with flash stimulation. However, we did find that DVD patients had significantly attenuated pattern reversal responses. The P100 components both to full-field stimulation and to half-field stimulation were significantly smaller in comparison with those of matched controls (Table 1). Most of the DVD patients (12/13, 92%) were amblyopic in one eye judged on clinical testing. All but one had no demonstrable binocular vision and on orthoptic testing had suppression. The patient who had the

Table 2 *Means and standard deviations (in parentheses) for the latency of the pattern reversal P100 following full-field and half-field stimulation*

Stimulus	*DVD patients*		*Matched controls*		*Significance level*
	Mean	*(SD)*	*Mean*	*(SD)*	
Binocular full-field	103·1	(4·8)	102·8	(2 5)	NS
Left eye full-field	102 4	(5·3)	104·4	(3 1)	NS
Right eye full-field	104·7	(6·6)	105·5	(3·5)	NS
Left eye left half-field	100·7	(7 6)	103·0	(3·3)	NS
right half-field	103·7	(7·2)	106·2	(3·8)	NS
Right eye left half-field	106·6	(5 5)	105·6	(3 0)	NS
right half-field	105·4	(7·9)	105·0	(3 0)	NS

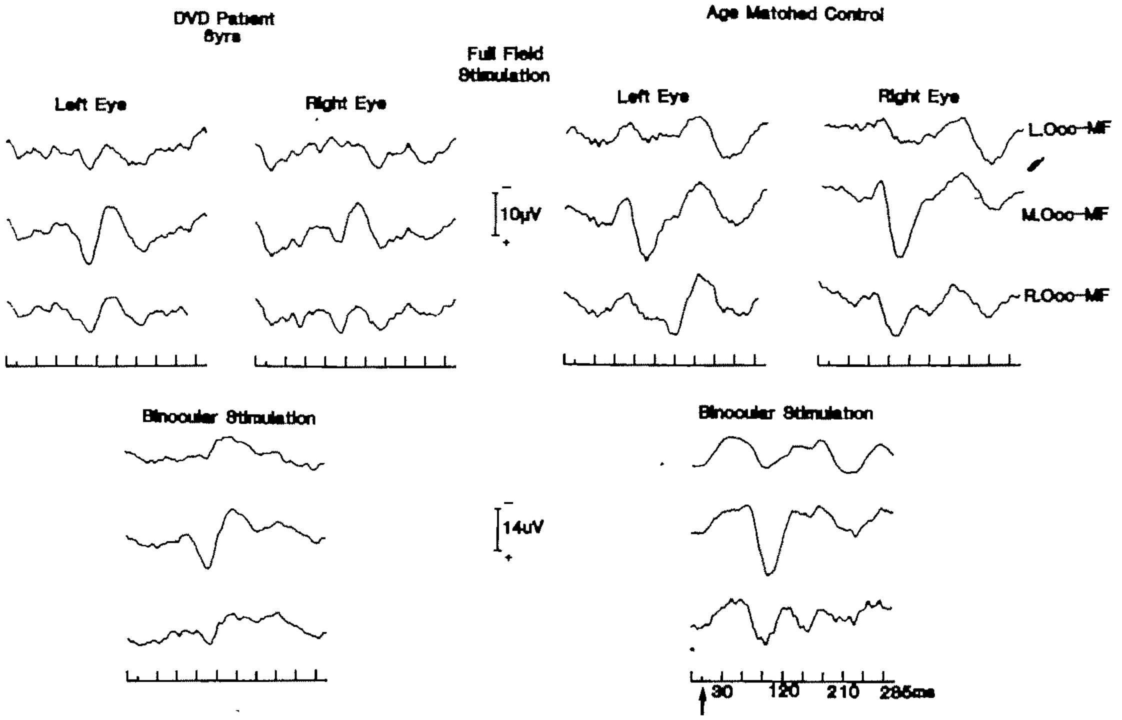

Fig. 3 *Monocular and binocular responses to full-field stimulation in a DVD patient (on the left) and an age matched control (on the right). Note the generally smaller responses from the DVD patient in comparison with the control.*

squint of later onset did show weak binocular vision with abnormal retinal correspondence. The degree of amblyopia was mild (within 2 Snellen lines of normal 6/6 level) in eight patients (62%), moderate (between 6/18 and 6/24) in three patients (23%), and marked (between 6/36 and 6/60) in two patients (15%). The full-field pattern P100 was commonly smaller in the amblyopic eye (mean 5·68 μV, SD 2·5) than in the fellow eye (mean 8·4 μV, SD 4·7), and this in part accounts for the significantly smaller responses in the DVD group. However, the mean full-field P100 amplitude from the non-amblyopic eye of DVD patients was markedly smaller (47% of the size) than the mean monocular amplitude of the control group (17·8 μV).

Fig. 3 shows (on the left side) monocular and binocular pattern VEPs in an 8-year-old boy with amblyopia in the right eye. His acuities were 6/36 for the right eye, 6/12 for the left, and 6/9 when viewing with both eyes. The VEPs from the amblyopic right eye were attenuated compared with those of the better-acuity left eye, but all pattern VEPs from the patient were smaller than those of the matched control (on right). The clear differences between the patient and control groups can be seen in Fig. 4, which shows the left and right eye pattern reversal P100 amplitude values of each patient together with the group mean (circled) and standard deviation.

Predictably, pattern VEPs to full-field binocular stimulation were also significantly smaller ($p<0.05$) than those of matched controls (Fig. 3 and Table 1), but the magnitude of the mean difference (32%) between the two groups was less than that for monocular stimulation conditions, in which the pattern response from the non-amblyopic eye was, on average, 53% smaller in comparison with either of the control eyes.

Discussion

We found no electrophysiological evidence, either from pattern or flash evoked potentials, to support Fitzgerald and Billson's[1] claim that patients with DVD have an anomalous (albinoid) visual pathway projection, in which not only all fibres subserving the temporal field of one eye cross at the chiasm but are accompanied by a significant proportion of fibres subserving the nasal half-field. Marked nasal/temporal half-field differences for the pattern reversal P100 component are reported to occur in both ocular and oculocutaneous albinism.[4] However, in the present study comparisons for the P100 following left

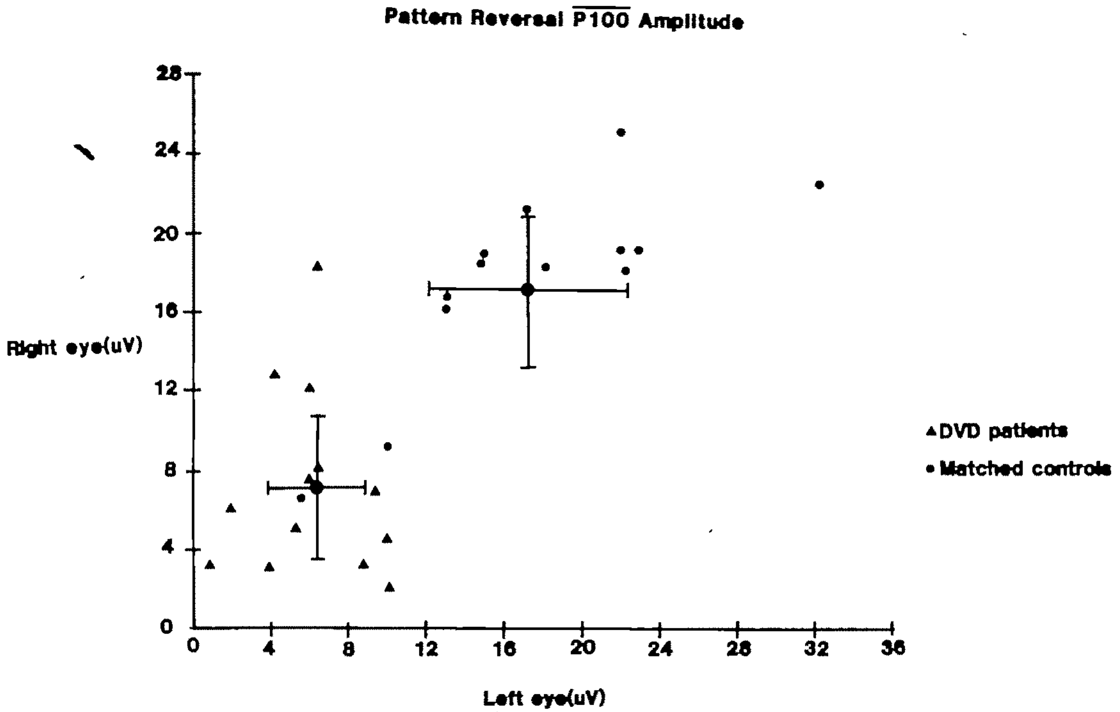

Fig. 4 *Graph of pattern reversal P100 amplitude following full-field stimulation for the right eye and the left eye. Both the individual data and means (circled) +1 standard deviation are shown. Note the DVD patients generally had smaller responses than age matched controls.*

and right half-field stimulation in DVD patients showed no significant amplitude differences. These negative findings were in line with the results following flash stimulation, which did not show differences for the comparison of responses from each eye recorded at the same lateral electrode. Such eye asymmetries are reported to occur in albino subjects.[2]

We also found no significant differences in the latency of the pattern reversal P100 when comparing DVD patients with matched controls. Fitzgerald and Billson[1] reported 'delayed' half-field responses in all patients with DVD. Carroll *et al.*[5] pointed out that it is possible to misidentify the second (commonly the largest) positivity of the paramacular complex (P135 component) as a delayed P100 component. In our study a relatively large half-field (0–14° eccentricity) was used, and this is known to be an effective stimulus size for eliciting not only the macularly derived P100 component, predominantly distributed over the side of scalp ipsilateral to the test half-field, but also in most subjects a contralateral paramacularly derived complex (P75, N105, P135) (see Blumhardt *et al.*[6] for full details). When the pattern reversal P100 component is attenuated, as we have shown for DVD patients, the paramacular complex with its commonly prominent P135 component can spread nearer the midline region and may be misidentified as the P100 component. Fitzgerald and Billson[1] did not address this possibility.

Our study showed that the pattern VEPs of DVD patients were generally significantly smaller than those of age matched controls. Two factors are likely to be involved in this effect. The first is amblyopia, which is known to be associated with conspicuous attenuation of pattern VEPs but not of pure luminance VEPs.[7] In our data the pattern reversal P100 component from the amblyopic eye was on average 70% smaller than that recorded from controls. The better-acuity eye of DVD patients produced larger pattern VEPs than the fellow amblyopic eye. However, responses from the good eyes were significantly attenuated compared with controls (53% smaller). A corollary of this was the significantly smaller binocular response from the patients than the controls. These findings are in line with those of Day *et al.*,[8] who used the swept spacial frequency technique to assess a group of infants with infantile esotropia and found subnormal acuity levels, estimated from VEP amplitude, for both monocular and binocular viewing conditions.

The second factor which is also probably contributing to attenuation of pattern VEPs in DVD is the latent nystagmus which is commonly associated with this condition. There appear to be no published studies of the effects of nystagmus on the recording of visual evoked potentials. We have found that pattern reversal VEPs to a 50-minute checkerboard are attenuated by, on average, 60% when recorded during horizontal vestibular nystagmus induced by a 40-second period of whole body rotation (Kriss A, *et al.*, report in preparation). Thus it is highly likely that latent nystagmus is contributing to the attenuation not only of monocular but also, to less extent, of binocular VEPs recorded from DVD patients. Although manifest latent nystagmus was not seen in any of our patients during binocular viewing, Dell'Osso *et al.*[9] have shown with sensitive eye movement recordings that most patients with monocular latent nystagmus show very small amplitude manifest latent nystagmus on binocular viewing.

It is conceivable that latent nystagmus may also be responsible for the anomalous pattern of asymmetry in the VEP reported by Fitzgerald and Billson.[1] In latent nystagmus there is a slow initial phase which is nasally directed followed by a faster jerk in the temporal direction. Whereas during nasal half-field testing the fovea drifts into the pattern field, for temporal half-field stimulation it drifts into a blank field. Gross *et al.*[10] found that pattern responses were markedly attenuated when elicited during a saccadic eye movement, but pure luminance responses were relatively unaffected. Consequently it is possible that nasal half-field responses may be relatively more attenuated than temporal half-field responses and thus produce a pattern of asymmetry similar to that observed in albinism. In this context it is relevant to note that in the present study both nasal field responses had, on average, smaller P100 components than the temporal half-field responses, though the difference was not significant. These minor nasal temporal differences did not appear in our control group.

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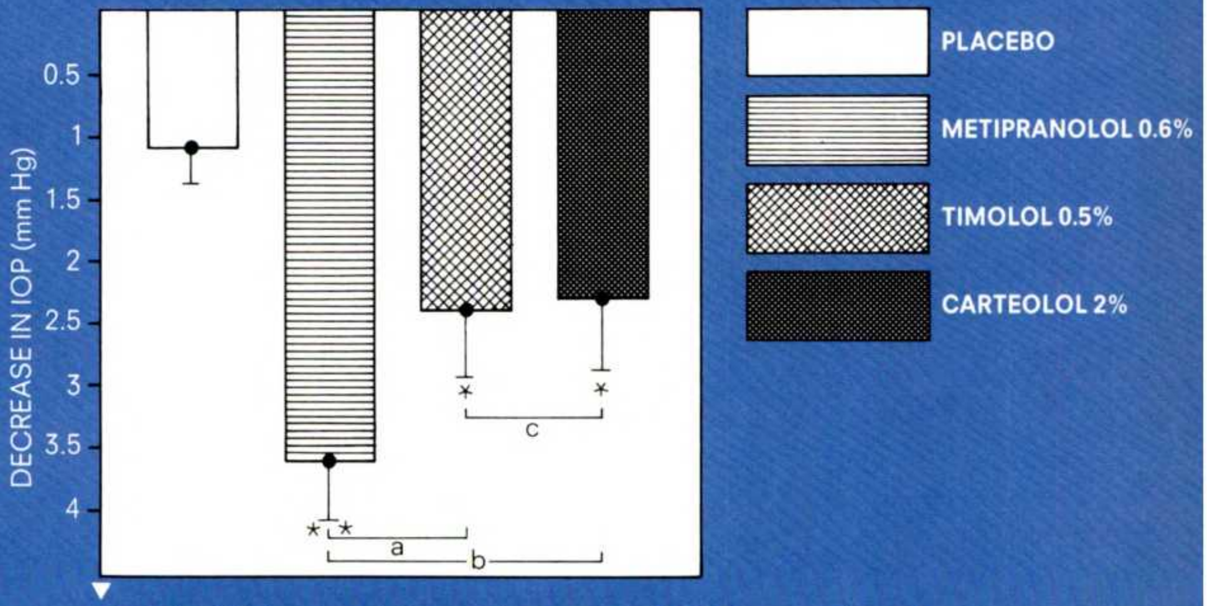
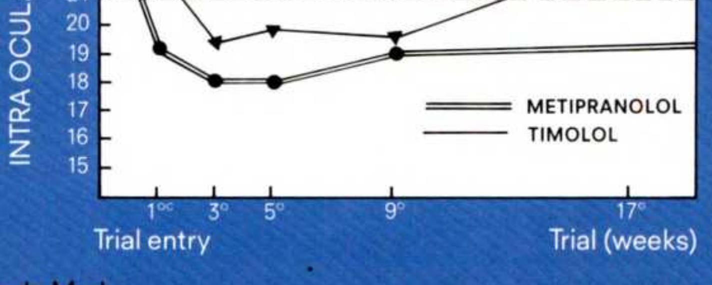


Mean (± SE) decrease in intraocular pressure *(IOP)* after one drop of ophthalmic β-blocker in each eye. (*$P < 0.01$; **$P < 0.001$ vs. placebo; a, $P < 0.01$; b, $P < 0.01$; c, NS.)

(b) In a middle term study[2]



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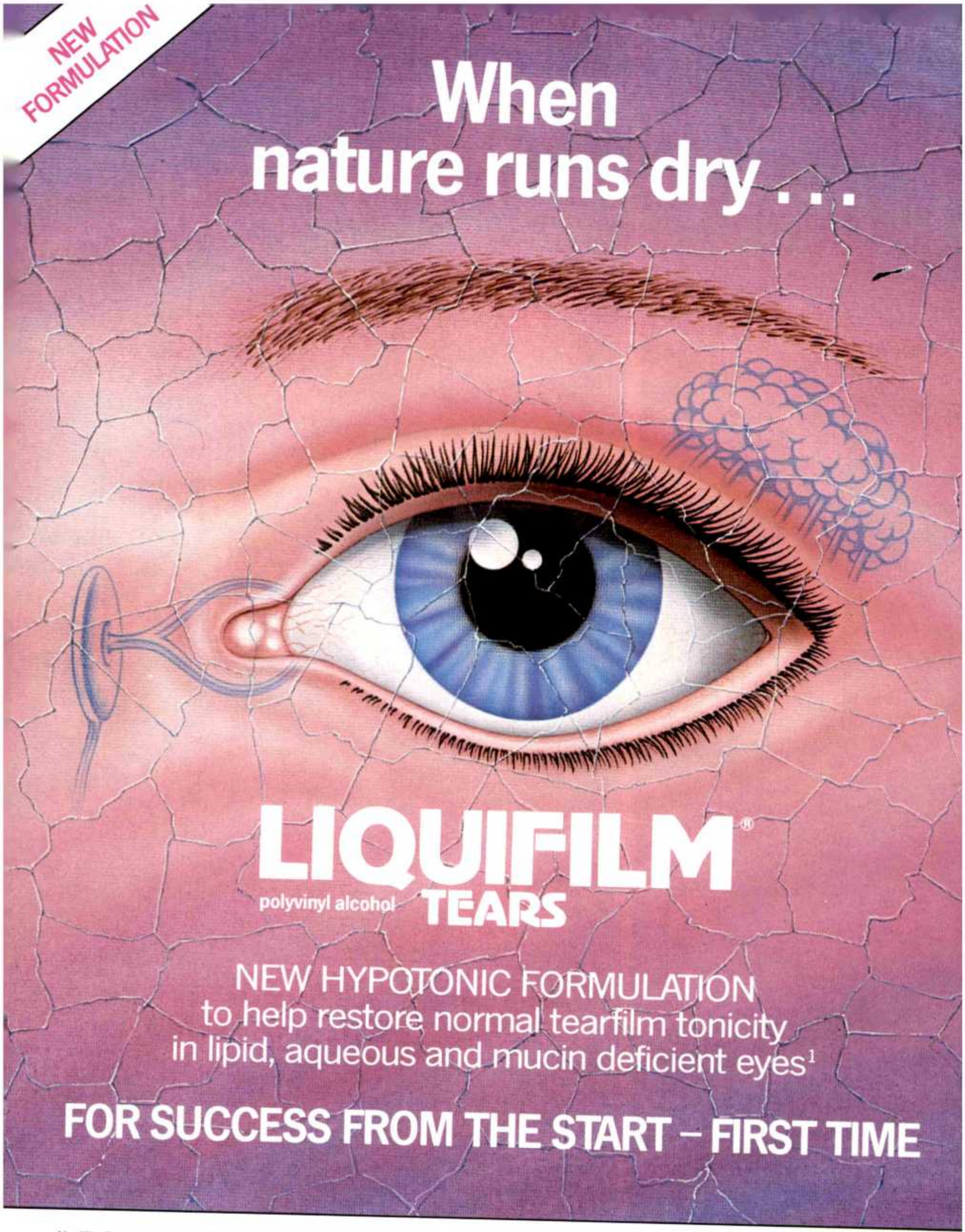
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Acanthamoeba keratitis associated with contact lenses: six consecutive cases of successful management

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SUMMARY We examined and treated six patients with acanthamoeba keratitis associated with contact lens wear from 1981 to 1988. Five patients were treated with topical neomycin-polymyxin B-gramicidin (Neosporin) and propamidine isethionate (Brolene) drops. The patients were followed up for an average of 32 months (range 16–75 months). Two patients underwent penetrating keratoplasty at 22 and 26 months after the onset of symptoms and have maintained clear grafts with no evidence of recurrence. In four patients corneal infiltrates cleared on topical medication. All six patients have 6/6 best corrected vision. Early diagnosis and medical treatment alone can result in resolution of corneal infiltrates due to acanthamoebae. With this initial therapy we have had no treatment failures.

Acanthamoeba keratitis has become an increasingly important problem.[1 2] A large majority of recently reported cases have occurred in contact lens wearers.[3 4] Initially recognised in wearers of soft contact lenses, acanthamoeba keratitis is now being reported in wearers of hard lenses, wearers of gas-permeable hard lenses and of Saturn II lenses. It is now well established that the probable source of the infection is contaminated home-made saline or tap water rinse. Efforts are now underway to educate colleagues and patients about the potential risks of these sources of infection.

Much knowledge has been gained about how to diagnose this infection rapidly, and therefore infections are now being diagnosed very early in their course. We have been using propamidine isethionate and neomycin-polymyxin B-gramicidin since 1984, when it was originally suggested to us by Peter Wright, and have had no treatment failures. While isolated cases have been successfully treated on a medical regimen alone, this is the first consecutive series of patients with acanthamoeba keratitis successfully treated by this regimen.

Case reports

CASE 1

This 13-year-old female, seen in December 1981, had an irritated right eye for one month. She wore daily-wear soft contact lenses for myopia. She made home-made saline from salt tablets and distilled water, and chemically disinfected the lenses every one to two weeks. She was treated with antibiotic drops by her referring ophthalmologist, who noted subepithelial opacities, a preauricular node, and a mild follicular conjunctivitis.

On our initial examination the visual acuity was 6/60 right eye and 6/6 left eye. There was marked epithelial mottling inferiorly without specific dendrite formation, underlying moderate stromal oedema, scattered nummular lesions in the anterior stroma both superiorly and inferiorly, and moderate keratic precipitates on the endothelium. The corneal sensation was decreased and there was moderate flare in the anterior chamber. The initial clinical impression was of herpes simplex keratitis. Over the next few months a ring infiltrate developed centrally with an overlying epithelial defect, leading to rapid melting of the anterior stroma. Six months later the cornea had become totally vascularised. In July 1983, 22 months after her initial symptoms, a penetrating keratoplasty was done to prevent perforation through a descemetocele.

Histological examination of the corneal button showed chronic granulomatous inflammation in the area of the ring infiltrate. No organisms were seen. Since April 1988 the patient has had a clear, compact graft, a best corrected visual acuity of 6/6 with a hard contact lens, and no clinical evidence of recurrence in

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the graft 4 years and 9 months after surgery.

Acanthamoeba keratitis was not suspected in this patient until 1984, when case 2 was diagnosed. The corneal button was re-examined; however, no cysts or trophozoites were found. Indirect immunofluorescent antibody staining was positive for *A. castellanii*. Saline solutions and contact lenses were not available for culture.

CASE 2

This 30-year-old female presented in July 1984 with a one-month history of presumed herpes simplex keratitis. She wore extended-wear soft contact lenses and made her own saline solution from salt tablets and distilled water. The lenses were removed every two weeks, cleaned with the saline solution, then reinserted.

Her visual acuity was 6/90 right eye and 6/6 left eye. The right cornea was oedematous. Anterior stromal infiltrates were concentrated over the visual axis and extending nasally in a dendritiform pattern. The corneal sensation was decreased, and there were a few keratic precipitates and only minimal cell and flare. She was treated for a presumed herpes simplex stromal keratitis.

One month later a dense anterior stromal ring infiltrate and a radial nerve infiltrate developed. Neomycin-polymyxin B-gramicidin four times a day was begun for suspected acanthamoeba keratitis. The ring infiltrate improved on this regimen. Two months later cultures of the cornea were positive for acanthamoebae. At Peter Wright's suggestion propamidine isethionate 1% (Brolene) was begun four times a day. Idoxuridine was stopped and the steroids were tapered. There was dramatic improvement in the ring infiltrate, and the vision improved to 6/24 with pinhole. All medications were stopped in March 1986, and by August there were no signs of recurrence. A penetrating keratoplasty was done 26 months after her initial symptoms. No trophozoites or cysts were seen in the corneal button with haematoxylin and eosin, periodic-acid-Schiff, and methenamine silver staining. However, immunofluorescent antibody staining was used to identify *A. castellanii*. Since April 1988 this patient has had a clear corneal transplant, a best corrected visual acuity of 6/6, and no evidence of recurrence in the graft, 20 months after surgery.

CASE 3

This 23-year-old female was seen in September 1986 with a four-day history of itching, burning, and mucous discharge from the left eye. She wore extended-wear soft contact lenses for two weeks at a time and cleaned them with a commercially prepared cleaner and enzyme tablets dissolved in a commercially prepared saline. She chemically disinfected the lenses once a month and cleaned the lenses with the enzymatic cleaner once a month. She alternated these two procedures so that each one was done once every two months. Immediately before putting the contact lenses in her eyes, she rinsed them in tap water.

The visual acuity with pinhole was 6/12 both eyes. There were multiple, hazy, grey-white anterior stromal infiltrates in the mid periphery of the left cornea in a semicircular pattern. The cornea was routinely cultured and the patient was treated for bacterial keratitis. Two days later there was a marked increase in the size and density of the stromal infiltrates. Acanthamoeba keratitis was suspected. However, because the epithelium was intact and the infiltrates deep, a corneal biopsy was done.

Smears from the base of the biopsy showed multiple, poorly staining, trophozoites on Gram and Geimsa stains. Histological examination of the biopsy gave negative results when examined with haematoxylin and eosin, methenamine silver, and periodic-acid-Schiff stains. Calcofluor white stain showed a few cysts on the posterior border of the biopsy specimen. The patient was started on propamidine isethionate and neomycin-polymyxin-gramicidin every 15 minutes and was admitted to the hospital for round-the-clock therapy. She stayed in the hospital three days and was then discharged on hourly therapy while awake and every two-hourly during the night. Two weeks later the corneal infiltrates had completely cleared, leaving faint scars.

Brolene and Neosporin were continued for one year four times a day initially and then gradually tapered to twice a day. Since April 1988 her cornea has been clear except for a scar at the biopsy site. The vision is 6/6 with spectacles. She had been off medication for seven months and there is no sign of recurrence. There has been no sign of active infection for 17 months.

CASE 4

This 25-year-old male presented in September 1986 with a history of pain, redness, watering, and a foreign body sensation in the right eye. He wore extended-wear soft contact lenses.

His visual acuity was 6/6 in both eyes. Examination of the cornea showed multiple tiny anterior stromal corneal infiltrates. The anterior chamber was deep and quiet and no other abnormalities were found. He was treated for presumed bacterial keratitis. However, one week later the infiltrates had progressed to diffuse patchy greyish white anterior stromal infiltrates in a semicircular pattern. The epithelium was intact and there was 2+ cell and flare in the anterior chamber.

Additional history revealed that during a camping trip his contact lens dried out and he had rehydrated it with well water and tap water on two separate occasions. A presumptive diagnosis of acanthamoeba keratitis was made based on the history of exposure to non-sterile solutions and the appearance of the corneal infiltrates, which were identical to the infiltrates in case 3. Propamidine isethionate and neomycin-polymyxin-gramicidin were started every 15 minutes and he was admitted to the hospital for three days of round-the-clock therapy. Three days later the drops were tapered to every 30 minutes while awake and every hour while asleep.

The drops were then slowly tapered to four times a day and then over the next 12 months tapered to twice a day and stopped. Since April 1988 he has continued to have 6/6 vision with spectacles. He has a clear cornea with some faint residual scarring in the mid periphery and has been off all medication for seven months, with no sign of recurrence. There has been no sign of active infection for the past 17 months.

CASE 5

This 31-year-old female presented in October 1986 with a one-week history of superficial keratitis in the left eye, unresponsive to topical antibiotics. Four weeks prior to that she had been switched from her soft contact lenses to Saturn II lenses. She used tap water which had been filtered through a micropore filter system to make her homemade saline. The visual acuity was 6/6 right eye and 6/24 left eye. Examination of the left cornea revealed a central patch of mottled, somewhat opaque, epithelium resembling confluent toxic epitheliopathy. The underlying stroma was clear, and there was moderate cell and flare in the anterior chamber. The remainder of the examination of both eyes was normal.

The initial clinical impression was presumed toxicity from either hydrogen peroxide or thiomersal (thimerosal). She was treated with antibiotic ointment and pressure patching. Two days later the epitheliopathy had increased and there were inflammatory cells in the anterior stroma. The cul-de-sac and cornea were cultured for acanthamoebae. The cultures from the cornea, the contact lens solutions, and the filtered tap water were positive for acanthamoebae. The cul-de-sac culture was negative. Propamidine isethionate and neomycin-polymyxin-gramicidin were started every hour round the clock.

Two weeks later the eye was white and the cornea was clear. The medications were gradually decreased to four times a day and then tapered over the next 12 months and stopped. Since April 1988 she has been off all medication for six months and has had no evidence of recurrence. There has been no sign of active infection for 16 months. The visual acuity is 6/6 with spectacles.

CASE 6

This 32-year-old female had been treated for herpes simplex keratitis in the left eye by her first ophthalmologist after developing symptoms in January 1987. When the keratitis did not improve, she was seen by a second ophthalmologist, who debrided the cornea twice and placed a bandage lens on the eye. When the keratitis did not improve with this regimen, she was referred to one of us.

The patient had worn hard contact lenses for many years. She stored her contacts in a home-made saline solution made from distilled water and salt tablets. Her jug of distilled water had been kept under the sink for at least two years. She soaked the lenses overnight in the home-made saline and washed them with a commercial cleaning preparation in the morning. She would then rinse them again with the home-made saline prior to insertion.

On examination in March her visual acuity was 6/6 right eye and 6/60 left eye. Centrally there was a large area of anterior stromal opacification. Within this area there were several nummular, denser anterior stromal infiltrates. There was a corneal nerve infiltrate at 7 o'clock.

The initial diagnosis of acanthamoeba keratitis was based on the radial nerve infiltrate and the history of home-made saline solutions. Since the epithelium was intact, the cornea was not scraped or cultured. Propamidine isethionate and neomycin-polymyxin-gramicidin were started every hour while she was awake. Cultures of the cul-de-sac were negative for acanthamoebae; however, cultures of the contact lens case and home-made saline were positive.

One month later the infiltrate had completely resolved, leaving a central corneal scar. The drops were decreased to four times a day and then tapered over the next 12 months. Since April 1988 her best corrected vision was 6/6 with a hard contact lens, and there has been no sign of recurrence or active infection for the past 16 months.

Discussion

Fortunately acanthamoeba keratitis is not rapidly progressive in comparison with some bacterial ulcers, and therefore it gives the practitioner a chance to intervene successfully even if symptoms and signs have been present for one to two weeks, or even one month. Intervening at the 1–4-week stage with topical propamidine isethionate and neomycin-polymyxin-gramicidin has proved to be effective in eliminating corneal infiltrates and maintaining a clear

Table 1 *Patient data*

Case	*Age/sex*	*CL, solutions*	*Initial diagnosis*	*Treatment*	*BCVA*	*Follow-up (months)*
1	13 F	DWSCL, ST and DW	Herpes simplex keratitis	Steroids, antivirals, antibiotics, PK at 22 months	6/6	75
2	30 F	EWSCL, ST and DW	Herpes simplex keratitis	Steroids, antivirals, antibiotics. Brolene and Neosporin at 5 months, PK at 26 months	6/6	46
3	23 F	EWSCL, commercial saline, TWR	Bacterial keratitis	Brolene and Neosporin at 1 week	6/6	20
4	25 M	EWSCL, WW, TW	Bacterial keratitis	Brolene and Neosporin at 1 week	6/6	20
5	31 F	Saturn II Lens, ST and TW	Bacterial keratitis	Brolene and Neosporin at 10 days	6/6	19
6	32 F	HCL, ST and DW	Herpes simplex keratitis	Steroids, antivirals, antibiotics. Brolene and Neosporin at 3 months	6/6	16

DWSCL=daily-wear soft contact lens EWSCL=extended-wear soft contact lens HCL=hard contact lens. ST=salt tablets DW=distilled water. TW=tap water. TWR=tap water rinse WW=well water PK=penetrating keratoplasty BCVA=best corrected visual acuity. Brolene (propamidine isethionate); Neosporin (neomycin-polymyxin-gramicidin)

cornea and useful vision in our series. Our results agree with those of earlier isolated case reports of successful medical treatment.[5,6]

Helpful clinical signs and history which may suggest an early acanthamoeba keratitis include the following: (1) previous treatment for herpes simplex heratitis with no improvement; (2) contact lens wear with exposure to home-made solution, tap water rinse, well water, intravenous saline; (3) bulbar injection but little chemosis and no discharge, mild to moderate lid oedema; (4) pain out of proportion to the clinical findings, infiltrates along the corneal nerves[7]; (5) epithelial irregularity or vesicular appearance in a pseudodendritic or linear pattern, epithelial haze, spherules, cystic lesions, refractile bodies, or recurrent epithelial erosions; (6) 0·5 mm diameter, white, discrete anterior stromal opacities, either single or multiple; (7) patchy anterior stromal greyish white infiltrates, multiple and variable in size, 1–3 mm with indistinct edges, forming a crescent or semicircular pattern; (8) stromal ring infiltrate or partial ring infiltrate (crescent).

Our initial treatment is intensive, and includes topical neomycin-polymyxin-gramicidin and propamidine isethionate every 15 minutes to every hour round the clock for three days, then every hour while the patient is awake and every two hours while asleep for three days, and then every hour while awake for another week. The drops are then tapered until a four times a day maintenance dose can be maintained. All patients on intensive topical medication will show signs of presumed drug toxicity. These include punctate epithelial erosions, an increase in bulbar conjunctival injection and chemosis, and a follicular response in the upper and lower tarsal conjunctival surfaces. This toxic response is reversible and should not influence or change the medical regimen.

Preliminary studies in our laboratory indicate that pentamidine and propamidine isethionate are amoebacidal in vitro and confirm previous study results.[5,8–10] Our rationale in the initial treatment of this keratitis is to saturate the cornea with the drug in an effort to kill trophozoites, to encourage encystment, and to maintain a drug level high enough to kill any emerging trophozoites should the cysts survive and later cause recurrence of the keratitis. We consider that delaying aggressive topical therapy could theoretically result in a significant increase in the number of organisms. A cornea which has been infected for 2–3 months may contain so many organisms that it is simply not possible to eradicate all of them with topical drops four times a day. This may account for some cases of reported failure of medical treatment.[11]

We do not use topical steroids because we consider that host defences are important in eradicating the organism and steroids inhibit neutrophil and macrophage response. The initial in-vitro study which reported that steroids inhibited morphogenesis of acanthamoeba organisms was not substantiated in subsequent animal studies[12] (Osato M, personal communication 1987). We therefore believe that inhibition of morphogenesis would probably not take place in the clinical situation and steroids should not be used in an effort to accomplish this.

Two of our patients underwent penetrating keratoplasty. The first patient was diagnosed in retrospect by examining the corneal button. This patient never received specific antiamoebic therapy, and so we do not consider this a medical failure. The surgery was performed 22 months after the presumed initial infection and was done for a threatening corneal perforation. By this time the keratitis appeared walled off, on both slit-lamp and histological examination, and therefore we do not consider this a surgical cure but rather a surgical solution to an optical and mechanical problem.

The second patient was misdiagnosed and treated with steroids, antivirals, and antibiotics for five months before the correct diagnosis was made. Specific antiamoebic therapy, propamidine isethionate and neosporin-polymyxin-gramicidin, was used for 15 months. Six months later, after no sign of recurrence off specific therapy, a penetrating keratoplasty was performed for optical rehabilitation, not therapeutic reasons. We consider this a case of successful medical treatment because the infection was arrested and controlled with specific topical medication and because there was no recurrence either before or after surgery when specific medication was discontinued.

We have shown that we have achieved consistently good results with this approach even though patients were treated at different times from the onset of their symptoms (Table 1). These results were achieved owing to a high level of suspicion and early appropriate medical therapy. We strongly recommend using this approach initially rather than resorting to a corneal transplant in an eye with an uncontrolled infection.

We thank Peter Wright, who has been a constant source of information and guidance on the medical treatment of acanthamoeba keratitis.

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Immunopathology of trachomatous conjunctivitis

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SUMMARY Upper palpebral conjunctival biopsy specimens obtained from eight patients with active trachoma were examined by routine histological and immunohistochemical methods. The epithelium expressed class I major histocompatibility complex (MHC) products throughout and class II MHC products in the superficial layers. The epithelial inflammatory infiltrate consisted of polymorphonuclear leucocytes, macrophages, T lymphocytes, and dendritic cells. In the underlying stroma the inflammatory infiltrate was organised as B lymphoid follicles, and there was also a diffuse infiltrate consisting of plasma cells and scattered B lymphoid cells, dendritic cells, T cells, macrophages, and polymorphonuclear leucocytes. Each type of cell has its special location in the tissue. Plasma cells were located on a subepithelial band and as a dense infiltrate round the acini of accessory lacrimal glands. IgA^+ plasma cells outnumbered IgG^+ cells, whereas IgM^+ and IgE^+ cells were few. Our data provide good evidence for the presence of both humoral and cell mediated immune responses and a possible role for autoimmune mechanisms in the conjunctival tissues of trachoma patients.

Trachoma is a chronic keratoconjunctivitis caused by *Chlamydia trachomatis* serotype A, B, or C.[1] It is one of the leading causes of blindness in underdeveloped countries and affects an estimated 500 million people.[2]

C. trachomatis is essentially a pathogen of mucosal surfaces, infecting and replicating within epithelial cells.[3] Ocular infection with the agent of *C. trachomatis* induces both humoral immunity[4-7] and cell mediated immunity.[8-10] The immune response seems to confer partial protection against subsequent infection, yet appears also to be responsible for much of the observed pathology and tissue destruction seen in trachoma.[11]

Analysis of the components of the local immune response occurring in the conjunctival tissues of patients with active trachoma has so far received relatively little attention. The disease is characterised histologically by the formation of large lymphoid follicles with prominent follicular centres in the stroma.[12] In the conjunctiva of monkeys experimentally inoculated with *C. trachomatis* these follicles were found to consist of B cells, T cells, and macrophages,[13] but no data are available from human material. Therefore, using the monoclonal antibody technique for the identification of cells involved in the immune response we analysed the in-situ immune reaction in trachomatous conjunctivitis in humans in order to examine more precisely the pathogenesis of this condition.

Subjects and methods

SUBJECTS

Eight patients presenting with active trachoma seen in the Ophthalmic Outpatient Clinic of Mansoura University Hospital were included in the study. All were examined by a slit-lamp, and corneal and conjunctival changes were recorded.

The patients comprised four males and four females. Their ages ranged from 3 to 9 years, average 5 years. Four patients were diagnosed clinically as trachoma stage 2a, three as trachoma stage 1, and one as trachoma stage 2b according to MacCallan's classification.[14] All the patients had upper limbal active pannus.

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METHODS

Upper palpebral conjunctival biopsy specimens were obtained from all the patients after informed consent. The specimens were immediately fixed for two to three hours in B_5 fixative composed of: (A) 90 ml distilled water, 6 g mercuric chloride, 2·074 g sodium acetate ($CH_3COONa.3H_2O$); and (B) 37% formaldehyde solution, pH 5·7. 9 ml of A and 1 ml of B were mixed immediately before use.

The specimens were then kept in absolute methanol until embedded in paraffin. Semiserial sections were cut and stained with haematoxylin and eosin for routine histology. Serial 6 μm sections were stained by a three-step indirect immunoperoxidase procedure[15] with the following monoclonal antibodies: MT_1, MB_2, LN_2, TAL-1B_5, and 3MA134.

MT_1 defines all T lymphocytes[16]; MB_2 defines all B cells, excluding mature plasma cells[16]; LN_2 identifies B cells, macrophages, interdigitating reticulum cells, and Langerhans cells[17]; TAL-1B_5 is directed against major histocompatibility complex (MHC) class II (HLA-DR) α chains[18]; and 3MA134 defines mononuclear phagocytes (Pulford *et al.*, unpublished data).

An unlabelled, three-step peroxidase-antiperoxidase (PAP) procedure[15] was applied for polyclonal antibodies directed against immunoglobulins A, G, M, and E as well as β_2-microglobulin

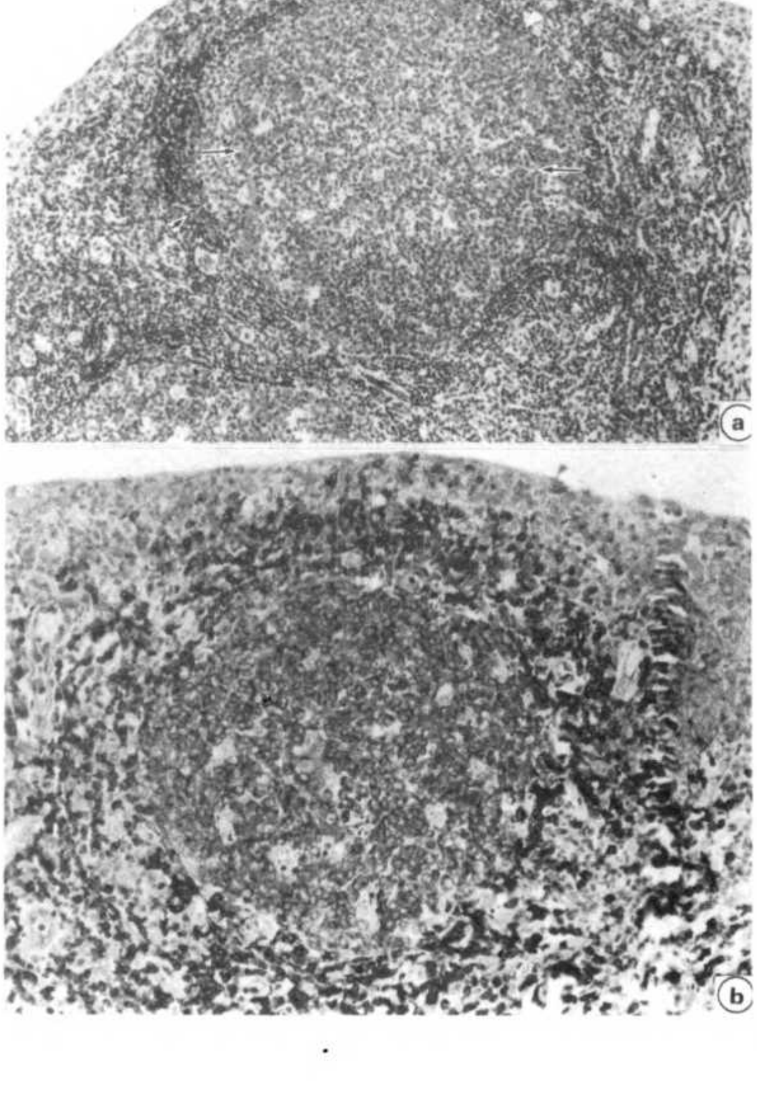

Fig. 1 (a) *Conjunctiva obtained from a patient with trachoma stage 2a showing secondary lymphoid follicle containing a large pale follicular centre (arrows) surrounded by a thin lymphocytic mantle (arrowheads). Haematoxylin and eosin, ×85.* (b) *MB_2 staining. Note that the lymphoid follicle and surrounding mantle are composed mostly of MB_2^+ B lymphocytes. Three-step indirect immunoperoxidase for MB_2, ×135.*

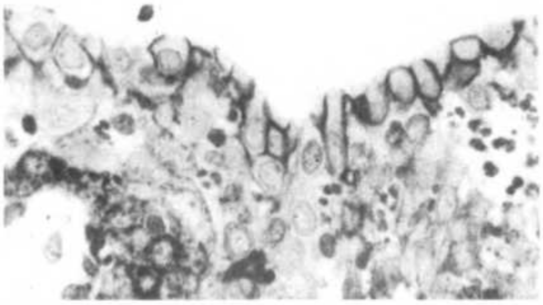

Fig. 2 *TAL-1B$_5$ staining shows membranous HLA-DR expression in the superficial epithelial layer. Three-step indirect immunoperoxidase for TAL-1B$_5$, ×385.*

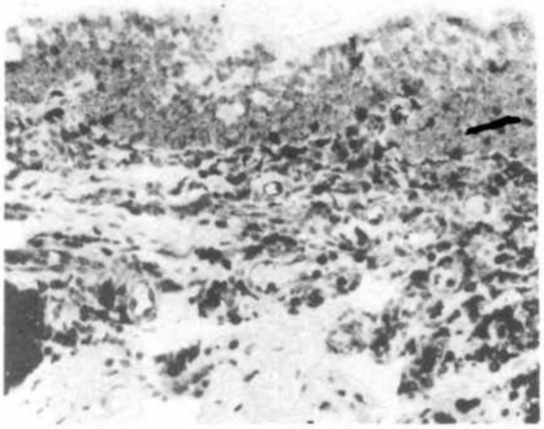

Fig. 3 *LN$_2$ staining. Note the presence of LN$_2$+ dendritic cells in the epithelium, in the underlying stroma, and at the interface between epithelium and stroma (arrow heads). Three-step indirect immunoperoxidase for LN$_2$, ×130.*

(b$_2$-m), which is a non-polymorphic part of the MHC class I.

Results

LIGHT MICROSCOPIC FINDINGS

All biopsy specimens showed comparable changes. The overlying epithelium showed mild to moderate hyperplasia, and was infiltrated by a mixed inflammatory infiltrate consisting of mononuclear and polymorphonuclear leucocytes. In the superficial epithelial layers variable numbers of Halberstaedter Prowazek inclusion bodies were seen.

In the underlying stroma, the inflammatory infiltrate was organised as lymphoid follicles and as a diffuse infiltrate. Variably sized secondary lymphoid follicles (Fig. 1a) containing a large, pale follicular centre surrounded by a lymphocytic mantle were seen throughout the biopsy specimens. The follicular centre was composed of small and large activated cleaved and non-cleaved lymphoid cells, and contained many stainable body macrophages. The surrounding lymphocytic mantle was thinned, and contained small darkly stained lymphocytes and lymphocytes of variable size and shape, indicating a progressive transformation.

In the area between the follicles and the epithelium, as well as in areas of diffuse inflammation, a mixed population of lymphocytes, polymorphonuclear leucocytes, macrophages, and some mast cells and eosinophils was observed. The blood vessels in these areas were distended and lined by prominent endothelium.

Finally, a band of plasma cells was situated directly underneath the epithelium, and a dense infiltration by plasma cells was observed also around the acini of accessory lacrimal glands.

IMMUNOHISTOCHEMICAL FINDINGS

All epithelial cells expressed β_2-microglobulin; membranous HLA-DR expression was noted mainly in the superficial epithelial layers (Fig. 2). The inflammatory infiltrate in the epithelium consisted of large numbers of 3MA134$^+$ macrophages, as well as variable numbers of MT$_1^+$ T lymphocytes and polymorphonuclear leucocytes. LN$_2^+$ HLA-DR$^+$ dendritic cells were observed in the deeper epithelial layers as well as in the underlying stroma (Fig. 3), where they were admixed with MT$_1^+$ T lymphocytes, 3MA134$^+$ macrophages, and scattered MB$_2^+$ lymphoid cells. Occasional dendritic cells were situated at the interface between epithelium and stroma.

The lymphoid follicles consisted of MB$_2^+$ LN$_2^+$ HLA-DR$^+$ B lymphocytes (Fig. 1b). In the follicular centre large 3MA134$^+$ stainable body macrophages (Fig. 4a), and some MT$_1^+$ T cells were observed (Fig. 4b).

In the subepithelial band of plasma cells (Fig. 5a) IgA$^+$ cells outnumbered IgG$^+$ cells, whereas IgM$^+$ and IgE$^+$ plasma cells were rare. A similar Ig distribution was found in the plasma cells populating the accessory lacrimal glands (Fig. 5b).

Discussion

Using in-situ immunohistochemical techniques and a panel of monoclonal antibodies we have analysed the cell populations involved in the immune response in the conjunctiva of patients presenting with active trachoma. Distinct compartments involved in humoral and cell mediated immune responses were observed.

The humoral immune response was represented by

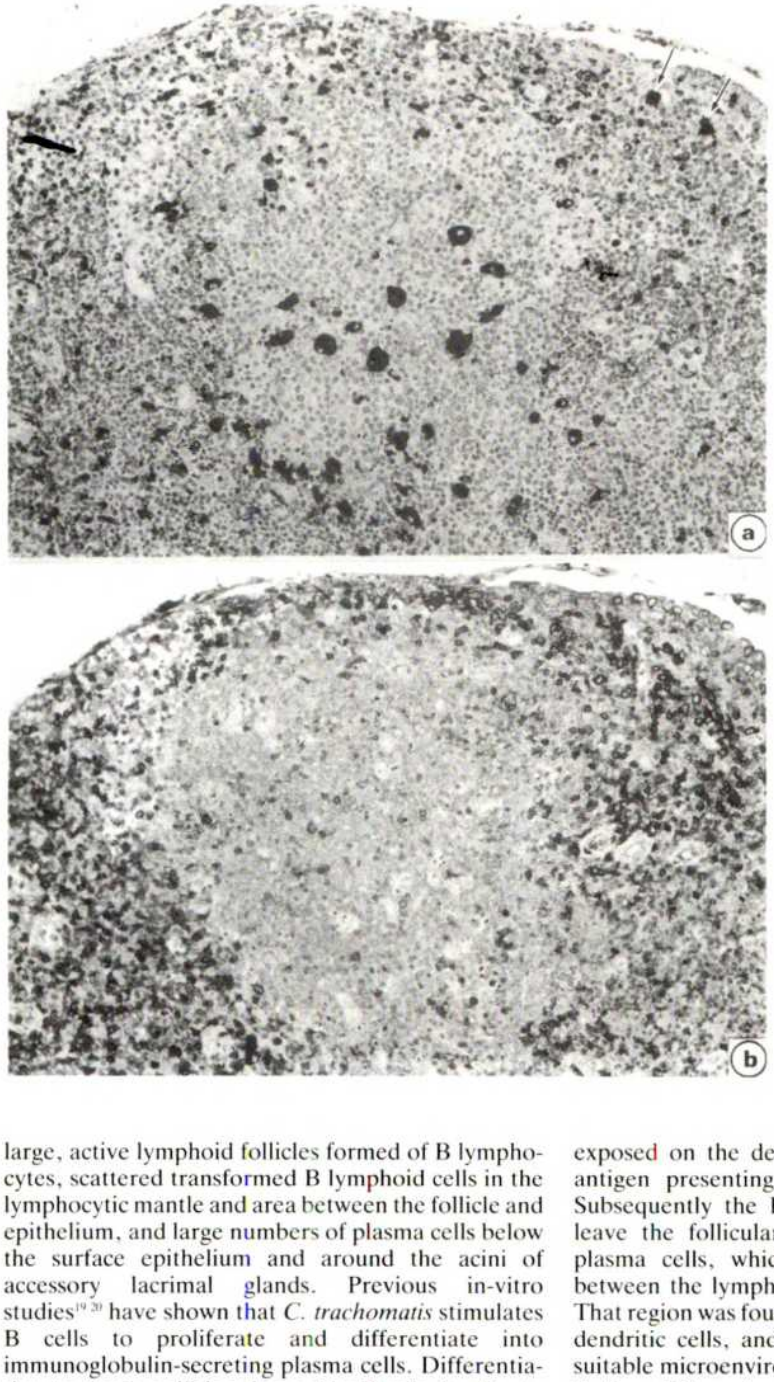

Fig. 4 (a) *3MA134 staining shows large immunoreactive macrophages in the follicular centre. Smaller $3MA134^+$ macrophages are present also in the surrounding infiltrate and in the epithelium (arrows). Three-step indirect immunoperoxidase for 3MA134, ×135.* (b) *MT_1 staining. Few MT_1^+ T lymphocytes are present in the follicular centre, whereas many T lymphocytes are present in the surrounding infiltrate. Three-step indirect immunoperoxidase for MT_1, ×135.*

large, active lymphoid follicles formed of B lymphocytes, scattered transformed B lymphoid cells in the lymphocytic mantle and area between the follicle and epithelium, and large numbers of plasma cells below the surface epithelium and around the acini of accessory lacrimal glands. Previous in-vitro studies[19,20] have shown that *C. trachomatis* stimulates B cells to proliferate and differentiate into immunoglobulin-secreting plasma cells. Differentiation to plasma cells is enhanced by T cells, leading to the secretion of large quantities of polyclonal immunoglobulins. Our results indicate that the in-vivo counterpart of this in-vitro response consists of B cells that are stimulated by chlamydial antigens exposed on the dendritic reticulum cells acting as antigen presenting cells in the follicular centre. Subsequently the B cells undergo transformation, leave the follicular centre, and differentiate into plasma cells, which migrate through the region between the lymphoid follicles and the epithelium. That region was found to consist mainly of T cells and dendritic cells, and it thus appears to represent a suitable microenvironment for the terminal differentiation of B lymphocytes into plasma cells.

IgA^+ plasma cells outnumbered IgG^+ plasma cells, whereas IgM^+ and IgE^+ plasma cells were conspicuously rare. These findings are in accordance with the detection of type-specific chlamydial IgA

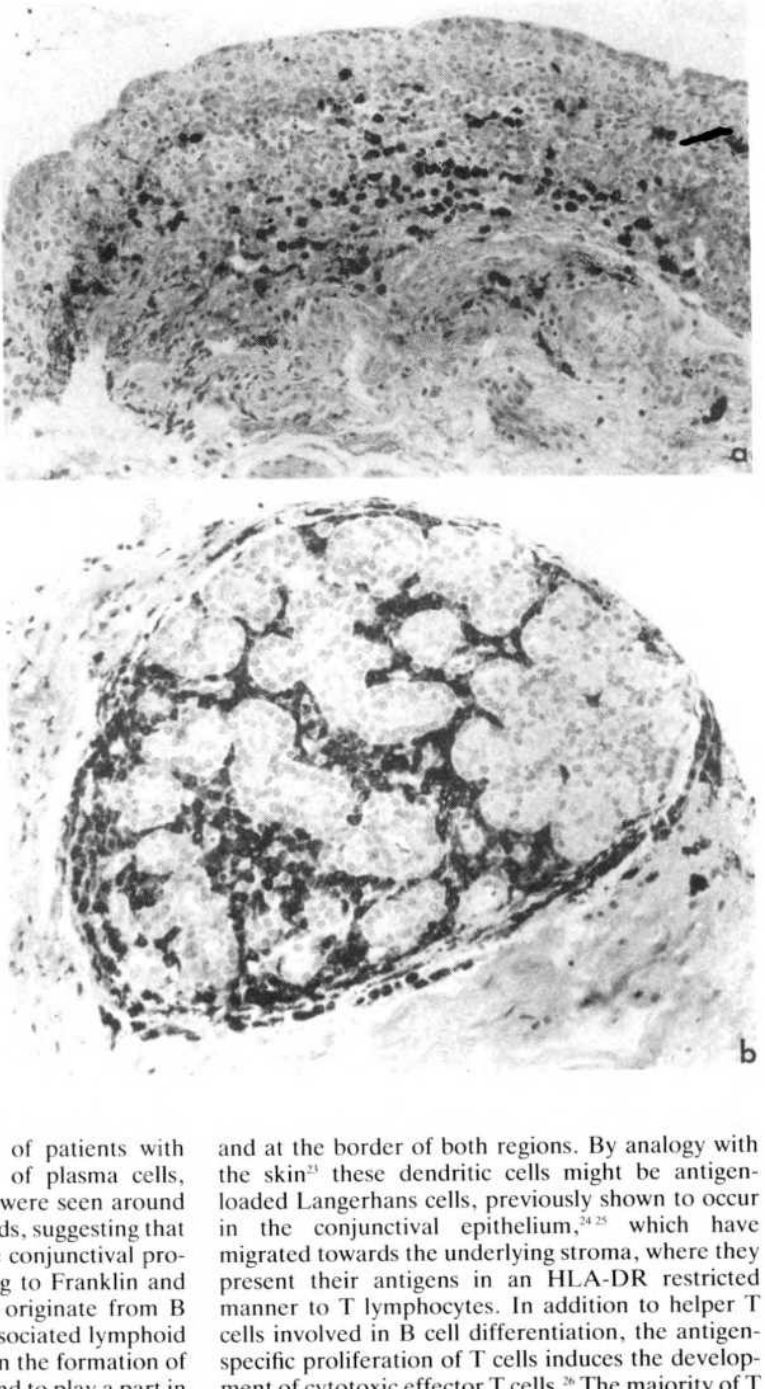

Fig. 5 (a) *IgA staining shows many IgA$^+$ plasma cells in a subepithelial band. PAP method for IgA, ×135.* (b) *IgA staining. Note the presence of dense accumulation of IgA$^+$ plasma cells around the acini of accessory lacrimal glands. PAP method for IgA, ×135.*

and IgG antibodies in the tears of patients with trachoma.[5] Dense accumulations of plasma cells, showing a similar Ig distribution, were seen around the acini of accessory lacrimal glands, suggesting that these glands constitute part of the conjunctival protective immune system. According to Franklin and Remus[21] these IgA$^+$ plasma cells originate from B cells present in the conjunctiva-associated lymphoid tissue (CALT), and are involved in the formation of secretory IgA, which has been found to play a part in the defence against chlamydial infection by preventing its adherence to epithelial cells.[22]

Scattered LN$_2^+$ HLA-DR$^+$ dendritic cells were observed in the epithelium, in the underlying stroma, and at the border of both regions. By analogy with the skin[23] these dendritic cells might be antigen-loaded Langerhans cells, previously shown to occur in the conjunctival epithelium,[24 25] which have migrated towards the underlying stroma, where they present their antigens in an HLA-DR restricted manner to T lymphocytes. In addition to helper T cells involved in B cell differentiation, the antigen-specific proliferation of T cells induces the development of cytotoxic effector T cells.[26] The majority of T lymphocytes present in the epithelium are likely to belong to the cytotoxic T cell subset engaged in cytotoxicity of infected cells. For the cytotoxic T cells to mediate cytotoxicity they must recognise class I

MHC antigen displayed by diseased cells.

The epithelial cells not only expressed the class I MHC associated β_2-microglobulin, but were also found to express HLA-DR antigens at their surface. HLA-DR antigens are present on cells involved in immune responses, including B cells, activated T cells, and antigen-presenting cells. The presence of HLA-DR antigens on these cells is associated with antigen recognition and presentation to T cells and the initiation of specific B and T cell responses.[27,28] We have shown that the normal conjunctival epithelium does not express HLA-DR antigens.[25] Its expression on the conjunctival epithelial cells in trachoma patients is probably due to the release of interferon-gamma by activated T cells present in the epithelium. Interferon-gamma has been shown to induce HLA-DR synthesis and expression by a variety of epithelial cells in vitro[29,30] and is produced by lymphocytes stimulated with *C. trachomatis*.[31] HLA-DR expression might allow conjunctival epithelial cells to present chlamydial antigens to T cells and thus to enhance the immune response in trachoma. Moreover, this HLA-DR expression may result in unopposed T cell proliferation and lead to perpetuation of the immune response. In addition, induction of HLA-DR expression on epithelial cells has been associated with autoimmune reactions—for example, autoimmune thyroiditis[32,33] and diabetes mellitus.[34] The epithelial cells expressing HLA-DR might present autoantigens to T lymphocytes which activate effector B and T lymphocytes, leading to induction of an autoimmune reaction.[35] In this context the appearance of autoantibodies in patients with chlamydial salpingitis[36] may be relevant.

Finally, considerable numbers of 3MA134$^+$ macrophages were observed in the epithelium as well as in the underlying stroma. Whereas most of these cells probably serve as scavenger cells involved in non-specific phagocytosis and degradation of cellular debris, a possible role as effector cells in cell mediated immunity to *C. trachomatis*, as suspected previously,[37] cannot be ruled out.

In summary, our data provide histological and immunohistochemical evidence for the development of both humoral and cell-mediated immune responses in the conjunctival tissue of patients suffering from trachoma. The role played by autoimmune mechanisms in this chronic infection needs further investigation.

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MT_1, MB_2, and LN_2 monoclonal antibodies were purchased from Biotest Seralc, Brussels, Belgium; TAL-$1B_5$ was a generous gift of Dr W F Bodmer, Imperial Cancer Research Fund, London; 3MA134 was a gift from Dr D Y Mason, Nuffield Department of Pathology, Oxford All polyclonal antibodies were obtained from Dakopatts a/s Denmark.

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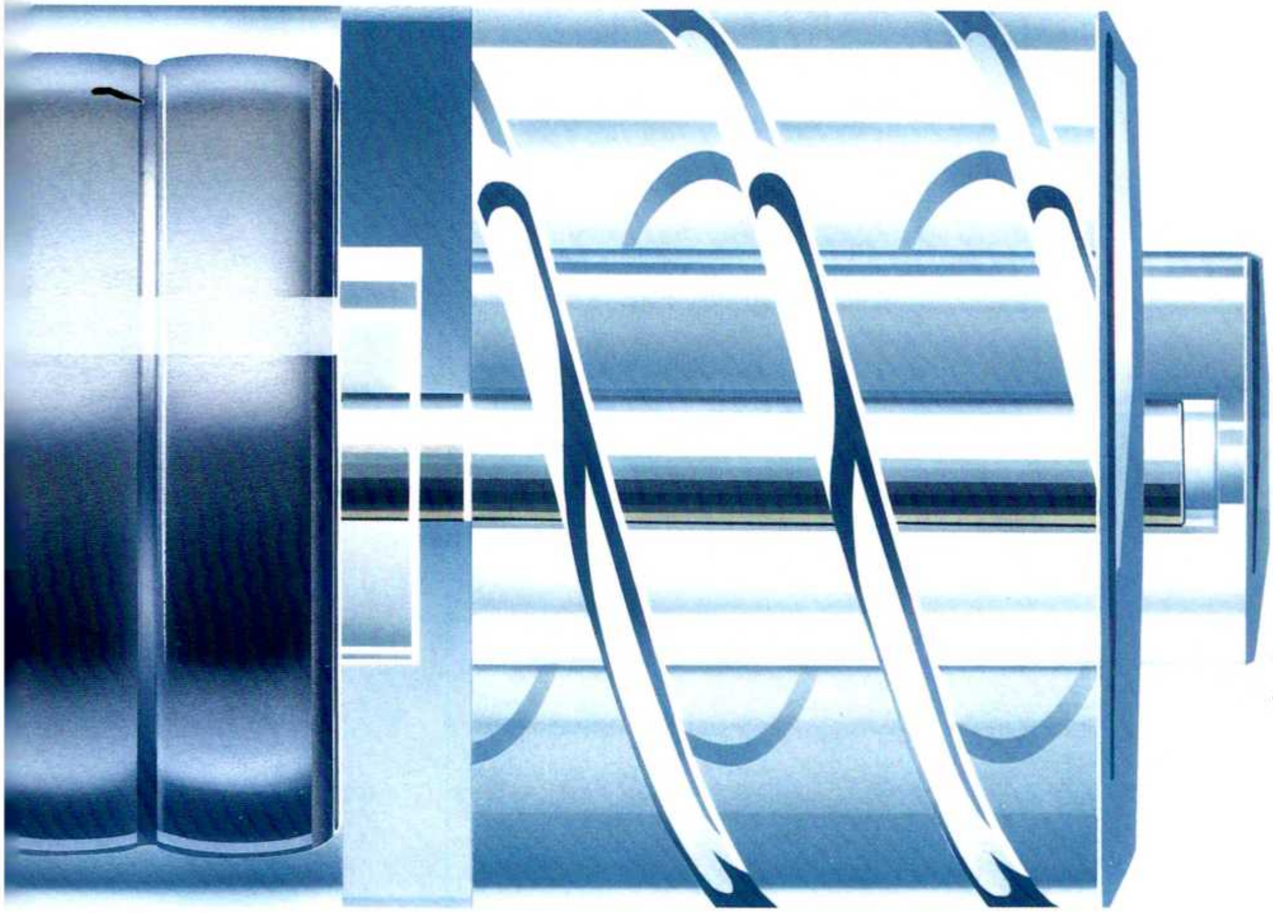

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Ptosis following cataract and trabeculectomy surgery

J P DEADY, N J PRICE, AND G A SUTTON

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SUMMARY A prospective study was carried out to estimate the incidence and severity of ptosis following cataract extraction and trabeculectomy. A postoperative ptosis of 2 mm or more was found in 6·2% of all cases. In this series the incidence of ptosis following surgery under local anaesthesia was greater than that under general anaesthesia. The aetiology and management of this complication are discussed.

The incidence of ptosis following ocular surgery has not been widely reported. Paris and Quickert defined postoperative ptosis following cataract extraction as 2 mm or more of drooping of the upper eyelid persisting for more than six months.[1] They asked 27 ophthalmologists about the frequency of this complication and derived estimates ranging from 0 to 10%, the most common estimate being 1 to 2%. In a study of patients undergoing cataract and glaucoma surgery, Alpar using the same criteria for ptosis found the incidence to be 11·4% following local anaesthesia and 1·5% following general anaesthesia.[2] From figures reported by Kaplan *et al.*[3] the incidence following cataract extraction under local anaesthesia would appear to be 13·5%.

The aetiology of postoperative ptosis is uncertain but thought to be a dehiscence or disinsertion of the levator aponeurosis during surgery. Paris and Quickert found disinsertion of the aponeurosis in two patients with ptosis following cataract extraction.[1] They suggested that prolonged upper lid oedema after surgery leads to disinsertion in older patients who have vulnerable aponeuroses. Aponeurotic defects may also be present in patients with involutional ptosis, some of whom have had previous orbital swelling, eyelid oedema, or blepharochalasis.[1,4–8] The main clinical features of ptosis due to a dehiscence or disinsertion of the levator aponeurosis are a high or absent lid crease, thinning of the ptotic eyelid above the tarsal plate, good or excellent levator function,[6] and deepening of the upper sulcus.[9]

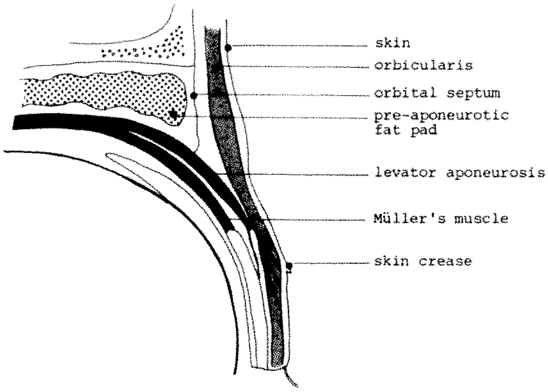

Fig. 1 *Upper eyelid. Normal anatomy.*

Opinion varies on the insertion of the levator aponeurosis.[10] Many authors regard the upper eyelid skin crease as being formed by fibres from the aponeurosis which are inserted into the skin. However, Collin *et al.*[9] showed that the upper eyelid skin crease is formed by the insertion of the levator aponeurosis into the septa between the orbicularis

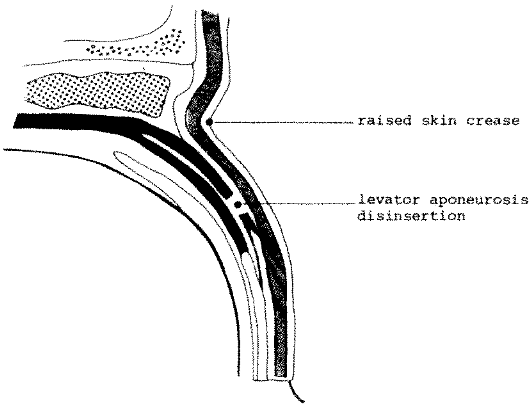

Fig. 2 *Upper eyelid. Levator aponeurosis disinsertion.*

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muscle bundles and not into the skin (Fig. 1). They reasoned that this would explain the high eyelid fold associated with a disinsertion of the aponeurosis. If the aponeurosis becomes disinserted or stretched, the original eyelid crease is lost and the levator retracts, pulling the orbital septum with it (Fig. 2). The orbicularis is pulled backwards, as it is firmly bound to the orbital septum. The eyelid skin follows the orbicularis, and a new higher eyelid crease is formed as the orbital septum is pulled into the orbit. This process is enhanced if the preaponeurotic fat pad is atrophic.[9]

Postoperative ptosis has been described as a significant complication of intraocular surgery.[3] Alpar stated that there may be a cosmetic and often functional defect,[2] which does suggest that in some cases the ptosis may be severe.

This prospective study was undertaken to investigate the incidence and severity of postoperative ptosis following cataract extraction and trabeculectomy.

Patients and methods

Consecutive patients were assessed on admission prior to unilateral cataract extraction or trabeculectomy. Excluded from the study were patients with a history of thyroid eye disease, external eye disease, or previous ocular or lid surgery on the preoperative side.

The following observations were made on both eyes before and after operation: (1) palpebral aperture in the primary position, (2) levator action, (3) height of the upper lid crease above the lid margin in downgaze, and (4) an assessment of the depth of the upper lid sulcus.

The following operative details were recorded: (1) surgical procedure, (2) type of anaesthesia, and (3) occurrence of a superior rectus haematoma. A superior rectus bridle suture was used in all procedures.

A pre-existing ptosis was defined as the difference between the palpebral apertures measured before surgery. We defined postoperative ptosis as a decrease of 2 mm or more in the palpebral aperture of the operated eye relative to the other eye persisting for at least six months after surgery in the absence of ocular or lid inflammation. The unoperated side therefore served as a control. Patients with a postoperative ptosis of 1 mm or more were reviewed for at least six months or until the ptosis had resolved if earlier. Any patients with postoperative ptosis who within six months required further surgery or were lost to follow-up were eliminated from the study.

Discrete data were compared by the χ^2 test with Yates's correction or, where the frequencies were smaller, Fisher's exact test. Semi-continuous data, such as relative change in palpebral apertures, were compared by the Wilcoxon rank sum test and corresponding medians and ranges quoted.

Results

One hundred and fifty patients were initially examined, and of these 140 completed follow-up. Of the 10 remaining patients four had a second surgical procedure, four were lost to follow-up, and two died. Six patients went on to have surgery on their second eye in the absence of ptosis following their first procedure. Thus 146 operations (116 cataract extractions and 30 trabeculectomies, 64 male and 82 female eyes, median age 72 years, range 23–97 years) were performed by six consultants and 15 surgeons in training.

The postoperative change in palpebral aperture varied from a decrease of 3·5 mm to an increase of 2 mm relative to the unoperated side. There was no postoperative ptosis in 70% (102 cases). The majority of the remaining 30% (44 cases) developed less than 2 mm of ptosis. The incidence of postoperative ptosis of 2 mm or more as previously defined was 6·2% (nine of 146 cases, 95% confidence interval 2·2–10·2%, median follow-up nine months).

Cases that developed postoperative ptosis had no pre-existing ptosis on the preoperative side. In contrast, they did have significantly more pre-existing ptosis on the unoperated side than those that did not develop ptosis ($p<0·001$).

We found no significant difference ($p>0·1$) between the median age of patients with postoperative ptosis (67 years) and those without (72 years). Although females accounted for 78% (seven of nine cases) of those with ptosis and 55% (75 of 137 cases) of those without, this difference was not found to be significant ($p>0·1$).

The incidence of ptosis following local anaesthesia (11·5%, three of 26 cases) was found to be higher than that following general anaesthesia (5%, six of 120 cases). However, the numbers of cases in these groups were insufficient to detect small significant differences.

Five patients had a superior rectus haematoma during placement of the bridle suture, none of whom developed ptosis. 18·5% (27 of 146 cases) developed at least 1 mm of ptosis, which later resolved (median follow-up seven months). 4·1% (six cases) developed ptosis which never exceeded 1·5 mm (median follow-up nine months). No patients had a ptosis which increased in severity within the follow-up period.

Levator function remained unaltered in patients with postoperative ptosis. An increase in height of the lid fold and deepening of the upper lid sulcus were difficult to assess. Although two patients with ptosis did show such changes, these occurred in patients without ptosis also.

Discussion

The incidences of postoperative ptosis following local and general anaesthesia in this study are similar to those found by others and we confirm a higher incidence following local anaesthesia.[2,3]

The fact that no eyes with pre-existing ptosis developed an increased ptosis postoperatively could be explained if a pre-existing aponeurotic defect had reached its maximum extent before surgery. Our finding that patients who developed a postoperative ptosis tended to have a pre-existing ptosis on the opposite side supports the theory that aponeurotic defects tend to become bilateral.[6] This group of patients with a vulnerable aponeurosis is at risk of developing postoperative ptosis.

Trauma or haemorrhage in the superior rectus muscle is one operative factor thought to result in postoperative ptosis.[2] Practically all patients who had a superior rectus haematoma were found by Alpar to develop postoperative ptosis,[2] but it is noteworthy that no patients in our study did so. Cataract surgery performed without a superior rectus bridle suture is said to be associated with a lower incidence of postoperative ptosis[3] (Bullock JD, personal communication, 1988).

In the evolution of postoperative ptosis the two cases reported by Paris and Quickert developed an increasing ptosis over 12 months.[1] Kaplan *et al.* also reported a worsening ptosis in 12% of postoperative patients over six months.[3] We had no cases of progressive ptosis. As 64·3% (27 of 42 cases) of ptoses of at least 1 mm resolved within six months in our study, we would agree with others that it would be prudent to wait at least six months[3] or until six months have elapsed without improvement[11] before contemplating surgery.

For small degrees of ptosis surgical correction is rarely indicated. Often elderly patients complain of ptosis only when it interferes with vision. It has not been ascertained how frequently postoperative ptosis requires correction for cosmetic or functional reasons, but in our study surgery has not been considered necessary.

Repositioning of the disinserted levator aponeurosis on the anterior tarsal plate is the preferred method of surgical correction in patients with this form of acquired ptosis and has been shown to give good results with minimal trauma to other lid structures.[1,6-8] This method allows for later adjustment of under- and overcorrections.[5] Others prefer Muller muscle-conjunctiva resection.[12,13] The Fasanella-Servat procedure[14] and its modifications,[15,16] although sometimes advocated for lesser degrees of this type of ptosis, would appear to be an inappropriate approach, as temporal overcorrections can occur,[4] and a failure to rectify the aponeurotic defect may result in late recurrences.[7]

The authors thank the consultant ophthalmic surgeons of the Birmingham and Midland Eye Hospital for permission to study their patients. We also thank Miss A E T Searle, FRCS, and Mrs C Rawlins for their assistance.

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Visual toxicity of synthetic retinoids

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SUMMARY Twelve patients treated with isotretinoin, a synthetic vitamin A analogue, were assessed before, during, and after therapy. Significant falls occurred in the amplitude of the a waves of the scotopic electroretinogram.

Vitamin A has been used topically and systemically in the treatment of skin disease for some 40 years.[1] Analogues of vitamin A (synthetic retinoids) have been developed which have a better therapeutic ratio than the vitamin, and these analogues are now widely used in dermatological practice. Symptomatic dry eye and blepharitis are well described side effects of these drugs,[2-4] but recent reports[5 6] suggest that these synthetic retinoids may interfere with retinal function.

This pilot study was set up to investigate prospectively the effect of synthetic analogues of vitamin A on visual function.

Patients and methods

Seventeen patients about to be treated with a synthetic retinoid preparation (isotretinoin) for a dermatological condition, were referred for a pretreatment assessment. This assessment included a full ophthalmic history and examination, visual field testing, electroretinography (ERG), electro-oculography (EOG), and dark adaptation (DA) studies. The patients were assessed again at one month and three months after starting treatment. The treatment was a four-month course, and it was intended that any subject showing abnormalities would be reassessed one month after stopping treatment; however, this was not always realised in practice.

One patient treated with another retinoid (etretinate) was included in the study and the results are presented separately.

Results

Of the 17 patients referred two failed to attend and three attended only once. Twelve patients were included in the study. No abnormality was seen in the EOG or DA assessments of any patient. Abnormalities were found in the a wave of the scotopic ERG to a white stimulus in some patients.

The results of the white scotopic ERG a and b waves are shown in Tables 1 and 2 respectively. The attendance is obviously far from satisfactory. Certain subjects show a drop in ERG amplitude in both a and b waves (for example, patient 9) from the pretreatment values to values found during treatment.

Only seven patients had attended for pretreatment assessment and at three months of treatment. These seven paired results (bold type in Tables 1 and 2) were analysed by the two-tailed paired *t* test. The analysis showed that the a wave results for both the right and left eyes showed a significant fall ($t=-2\cdot60$ and $t=-2\cdot80$ respectively, with 6 degrees of freedom, $p<0\cdot05$). The b wave changes, however, were not significant ($t=-1\cdot47$ and $t=-1\cdot67$).

Table 1 *a Wave ERG values (microvolts)*

Patient	*Pre-Rx*		*At 1 month's Rx*		*At 3 months' Rx*		*Post-Rx*	
	R	*L*	*R*	*L*	*R*	*L*	*R*	*L*
1			180	180	200	210		
2					240	200	100	170
3	**200**	**180**			**280**	**240**	260	280
4	**260**	**260**	260	240	**160**	**170**		
5			325	340	200	220	320	165
6			160	140	180	200	170	130
7	**460**	**460**			**360**	**330**		
8	**240**	**380**	220	200	**160**	**180**		
9	**340**	**370**	230	250	**210**	**250**		
10	**300**	**300**	200	200	**250**	**260**		
11	**220**	**200**	260	280	**120**	**120**		
12	200	220	180	180				

Rx=treatment

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Table 2 *b Wave ERG values (microvolts)*

Patient	*Pre-Rx*		*At 1 month's Rx*		*At 3 months' Rx*		*Post-Rx*	
	R	*L*	*R*	*L*	*R*	*L*	*R*	*L*
1			404	400	420	432		
2					460	468	348	460
3	**544**	**484**			**600**	**584**	620	608
4	**408**	**452**	476	436	**408**	**412**		
5			492	488	312	236	416	364
6			376	356	380	380	355	290
7	**612**	**596**			**648**	**588**		
8	**472**	**624**	496	412	**272**	**332**		
9	**496**	**544**	350	332	**364**	**408**		
10	**656**	**616**	568	520	**504**	**524**		
11	**464**	**404**	420	468	**344**	**352**		
12	360	380	330	306				

Rx=treament

The one patient (13) using etretinate showed a large and sustained drop in both a and b waves which has not markedly improved since stopping treatment (Table 3). This fits well with the known pharmacodynamics of this drug.

STATISTICS

The standardisation of electrophysiological tests is not easy, and we have therefore resisted the temptation to compare our results with those from a group of 'normal' patients, despite such a procedure giving larger numbers to work with. By restricting the analysis of data only to those patients who have results for the pretreatment and the three months of treatment assessments it was hoped to reduce some of the variability in these tests.

Discussion

'Retinoid' is a generic term describing naturally occurring compounds with vitamin A activity, and synthetic analogues with or without the biological activity of retinol. Vitamin A is vital to many systems in the body, including the maintenance of epithelia, spermatogenesis, and mucus secretion as well as in vision.[7]

Table 3 *Patient taking etretinate a and b wave ERG values (microvolts)*

Patient 13		*Pre-Rx*	*On treatment (4/12 duration)*		*Post-Rx*	
			1/12	*3/12*	*1/12*	*3/12*
a Wave	R	180	160	100	110	100
	L	160	140	104	110	120
b Wave	R	320	304	214	220	260
	R	280	286	272	214	230

Rx=treatment.

Different metabolites may be involved in different tissues. Certainly it is well known that the conformational change of 11-cis-retinal to the all trans form is an essential step in vision. That different metabolites are involved is supported by the observed differences in side effects of different analogues and by the fact that, when given to retinol deficient animals, retinoic acid can support epithelium, but *not* spermatogenesis or vision.[8] Many analogues of retinol with a greater or lesser degree of vitamin A activity have been synthesised, and it is not unreasonable therefore to suspect that some of these analogues may interfere with visual function while acting as vitamin A substitutes in other tissues.

Retinol is involved in the functioning of the photoreceptors and so one might expect the primary components of the ERG (early receptor potential and a wave) to be affected more than the later components (b wave). This fits with our data where a wave but not b wave changes occur. Some of our subjects show suggestive changes in the b wave, and with larger numbers there might prove to be significant falls in this component of the ERG. The early receptor potential was not looked at in this study, but changes have been reported with etretinate suggesting disturbance of the primary photochemical process.[9]

While isotretinoin has a fairly short half life, etretinate is stored in fat and has a prolonged effect.[10] The one patient taking etretinate has shown a correspondingly prolonged reduction in his a and b wave amplitudes.

In view of the large number of patients taking these drugs it is impractical to screen them all for visual toxicity. However, until the effects of these synthetic analogues of vitamin A are better understood, we suggest that any patients complaining of difficulties in night vision or with colour vision abnormalities’ should be reviewed. Certainly patients in those occupations where reduced night vision or colour sensitivity would be a problem, such as the armed forces or merchant seamen, may well require more detailed observation.

Dr M A Cowan and Dr K S Ryatt kindly allowed their patients to take part in this study. Thanks are due to the Retina Department of the Birmingham and Midland Eye Hospital for performing the electrodiagnostic and psychophysical tests.

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Familial iris melanosis—a misnomer?

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SUMMARY Iris melanosis is an unusual condition characterised by the presence of minute, discrete, pigmented elevations arising from the anterior surface of the iris. We encountered two unrelated Mexican families in which all children, but no parent, had varying degrees of the condition bilaterally. Some family members also gave findings suggestive of ocular hypertension. No family member had any other ocular or cutaneous pigmentary changes with the exception of a hairy naevus on the thigh of one member. To our knowledge these are the first families reported with more than one member having isolated iris melanosis. This is also the first report of a possible relationship with ocular hypertension. Finally we suggest that the term 'melanosis' may be a misnomer, since the condition is characterised not by abnormal iris hyperpigmentation but by discrete, round elevations on the anterior iris surface.

Iris melanosis is an unusual condition characterised by minute, discrete, pigmented elevations arising from the anterior surface of the iris.[1-4] Although it usually is unilateral, a bilateral case was recently described.[4] The entire iris surface or just a sector may be involved. Iris melanosis, as opposed to the more generalised ocular melanosis, is not associated with any other ocular, cutaneous, or systemic abnormalities. While most cases of generalised ocular melanosis are sporadic, an autosomal dominant mode of inheritance has been suggested.[1]

We present here what is to our knowledge the first two family pedigrees for iris melanosis, as well as the first report of a possible association with ocular hypertension.

Material and methods

Our study is based on two families in which iris melanosis was present in all children but in none of the parents. Both families were Mexican but were from different parts of Mexico and were unrelated to each other (Figs. 1, 2). Each of the family members underwent a complete ophthalmic examination (Tables 1, 3), including best corrected visual acuity, manifest refraction, slit-lamp examination of the anterior segment, Goldmann applanation tonometry, slit-lamp gonioscopy (family A only), and dilated fundus examination. Goldmann visual fields were performed on three of the children in family A (patients II-3, II-4, and II-6). In addition home tonometry was performed on these three patients using a self-tonometer as described elsewhere.[7] Tonometry readings were obtained on three to nine separate days during a one-month period, with three random measurements performed on each day (Table 2). Finally, a detailed history regarding skin lesions or systemic diseases was obtained.

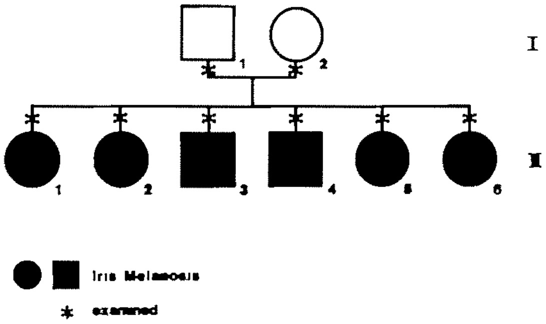

Fig 1 *Pedigree of family A Squares indicate male members; circles indicate female members.*

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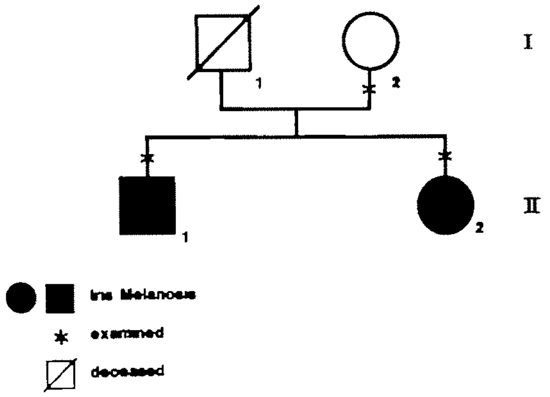

Fig. 2 *Pedigree of family B. Squares indicate male members, circles indicate female members.*

Results

FAMILY A

Family A comprised six siblings (two males, four females) ranging in age from 13 to 27 years (Table 1). Both parents were Mexican, and there was no known consanguinity. Best corrected visual acuity was 20/20 in all family members, with plano, myopic, or mixed astigmatic refractive errors. Applanation tonometry revealed intraocular pressures of 20 mmHg or greater in three children (patients II-3, II-4, and II-6). These patients then underwent home tonometry, which revealed abnormal pressure elevations in patients II-3 and II-4 (Table 2). Patient II-4 had a maximum intraocular pressure of 27 mmHg OD and 26 mmHg OS, while patient II-3 had maximum pressures of 24 mmHg OD and 25 mmHg OS. Slit-lamp gonioscopy gave normal results except for the father and patient II-6, who both had prominent iris processes. None of the patients had abnormal angle pigmentation or angle maldevelopment.

Table 2 *Home tonometry measurements in family A*

Patient	*Number of days tested*	*Maximum IOP (mmHg)*	
		OD	*OS*
II-3	9	24	25
II-4	7	27	26
II-6	3	20	22

Slit-lamp examination disclosed no abnormal eyelid, conjunctival, fundus, or scleral pigmentation in any of the family members. The irides of the children were brown and contained minute, discrete, pigmented elevations on the anterior surface (Figs. 3, 4). The extent of involvement varied from as many as 30 to 40 excrescences per clock hour of iris (Fig. 3) to as few as one to five per clock hour (Fig. 4). These excrescences tended to be more concentrated on the midperipheral and inferior portions of the iris (Table 1). The disease was bilateral and symmetrical. The mother's irides were brownish green and had no pigmented elevations (Fig. 5). The father's irides were brown, with a smooth anterior surface. Two flat iris freckles, with a smooth anterior surface, were noted (Fig. 6).

Fundus examination disclosed no abnormal choroidal pigmentation. Cup-to-disc ratios were within normal limits except for patient II-6, who had a moderate amount of asymmetry (Table 1). Goldmann visual fields were full in those family members tested (patients II-3, II-4, and II-6).

No family member had any known abnormal skin pigmentation.

Table 1 *Ocular findings in family A*

Patient/age (yr)/sex	*Visual acuity (OU)*	*Refraction*	*IOP (mmHg)*	*Gonioscopy*	*Iris involvement*	*Other*
II-1/27/F	20/20	Plano OU	17 OU	Normal	Moderate, midperipheral, more inferiorly OU	C/D 0 30 OU
II-2/23/F	20/20	Plano OU	18 OU	Normal	Mild, midperipheral OU	C/D 0 30 OD, 0 25 OS
II-3/21/M	20/20	−3 50+0 50×90° OD −2 25+0 25×105° OS	24 OD 22 OS	Normal	Mild, inferiorly only OU	C/D 0 30 OU, full GVF
II-4/19/M	20/20	Plano OU	20 OU	Normal	Moderate, midperipheral OU	C/D 0·30 OU, full GVF
II-5/18/F	20/20	−1 75 sphere OU	18 OU	Normal	Mild, midperipheral, more inferiorly OU	C/D 0 20 OU
II-6/13/F	20/20	−2 25+2·25×90° OD −3·50+2·50×90° OS	22 OD 20 OS	Prominent iris processes OU	Extensive, entire anterior surface OU	C/D 0 25 OD, 0·50 OS; full GVF
I-2/48/F	20/20	−0·75 sphere OU	18 OU	Normal	None	Breast carcinoma metastatic to choroid
I-1/54/M	20/20	−0·50 sphere OD −0·75+0·50×80° OS	18 OU	Prominent iris processes OU	2 Brown freckles, no discrete elevations	

OU=both eyes IOP=intraocular pressure OD=right eye. OS=left eye C/D=cup-to-disc ratio GVF=Goldmann visual fields.

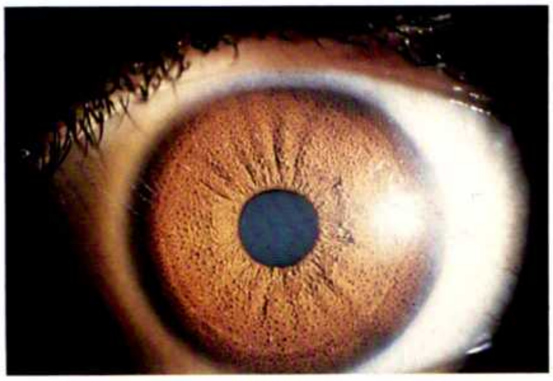

Fig. 3 *Iris of patient II-6 (family A) showing numerous minute, discrete, pigmented elevations on the anterior surface.*

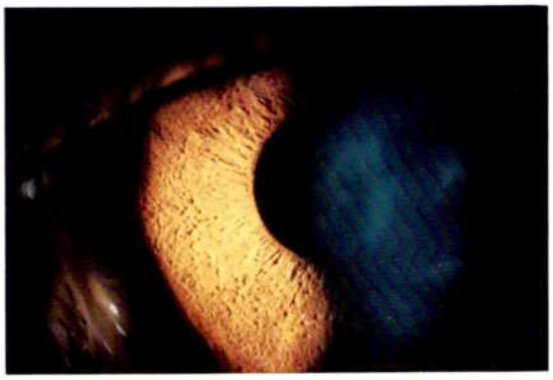

Fig. 4 *Iris of patient II-4 (family A) showing fewer iris excrescences than his sister (Fig. 3). They tend to be more concentrated on the midperipheral and inferior iris.*

FAMILY B

Family B comprised two children, a boy aged 13 years and a girl aged 8 years (Table 3). Both parents were Mexican, and there was no known consanguinity. The father was deceased. Best corrected visual acuity was 20/25 or better, with myopic or mixed astigmatic refractive errors, in all family members. Applanation tonometry revealed normal intraocular pressures.

Slit-lamp examination disclosed no abnormal eyelid, conjunctival, scleral, or fundus pigmentation in any family members. The irides of the children were brown and contained minute, discrete, pigmented elevations of the anterior surface. Patient II-1 had extensive involvement of the entire midperipheral iris with 20 to 30 excrescences per clock hour of iris (Fig. 7), while his sister (patient II-2) had only a few excrescences along the inferior midperipheral iris. Involvement was bilateral and symmetrical. The mother's irides were brown with a smooth anterior surface.

Fundus examination revealed no abnormal pigmentation and a normal cup-to-disc ratio. Patient II-1 had a hairy naevus on his left thigh.

Discussion

Melanosis of the eye (melanosis oculi) refers to increased pigmentation of the iris, ciliary body, and choroid, as well as the sclera, conjunctiva, and optic disc.[1] It may exist in two forms, either congenital or acquired. Iris melanosis was first described by Coats in 1912 as a unilateral iris condition in which the iris 'anterior surface is sown all over with minute, discrete, hemispherical, pigmented prominences, arranged quite regularly, the appearance being comparable with "goose-skin" or the surface of a golf ball'.[2] He found an otherwise normal function of the eye, including visual acuity and pupillary reactions. He believed the condition to be non-progressive, though the more generalised ocular melanosis may be associated with an increased risk of uveal

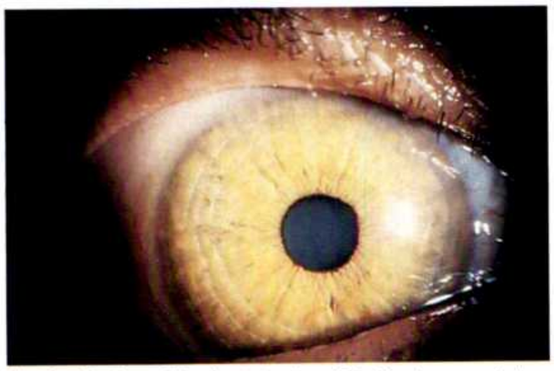

Fig. 5 *Mother of family A (patient I-2). She has greenish brown irides with no abnormal iris excrescences.*

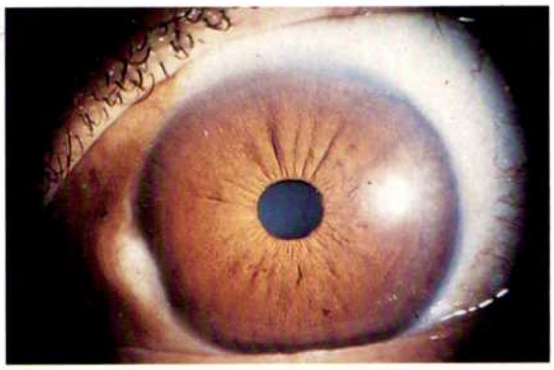

Fig. 6 *Father of family A (patient I-1). He has brown irides with a smooth anterior surface.*

Table 3 *Ocular findings in family B*

Patient/age (yr)/sex	*Visual acuity (OU)*	*Refraction*	*IOP (mmHg)*	*Iris involvement*	*Other*
II-1/13/M	20/25	−3·00 sphere OU	10 OU	Extensive, midperipheral OU	C/D 0·20 OU, hairy naevus on left thigh
II-2/8/F	20/25	−1·75 sphere OU	12 OU	Mild, midperipheral, more inferiorly OU	C/D 0·10 OU
I-2/32/F	20/20	−1·50+1·25×180° −2·00+1·25×180°	10 OU	None	C/D 0·10 OU

OU=both eyes. IOP=intraocular pressure. C/D=cup-to-disc ratio.

malignant melanoma.[2,3] No relationship between race and risk of malignancy was discovered for iris melanosis. While most cases of generalised ocular melanosis occur sporadically, autosomal dominant and recessive forms of transmission have been described.[1]

Other authors have noted a sectorial involvement of the iris by these 'evenly distributed small mamillations with bases radiating in minute folds'.[5,6] Recently, Traboulsi and Maumenee described a single case of bilateral iris melanosis without other ocular or systemic involvement or family history.[4] They claim that this was the first reported case of bilateral iris melanosis.

We have described two Mexican families in which all children but none of the parents have varying degrees of discrete, pigmented elevations of the anterior surface of each iris. The extent of involvement varies from as many as 30 to 40 to as few as one to five protuberances per clock hour of iris. These protuberances tend to be more concentrated in the midperipheral and inferior iris. Involvement is bilateral and symmetrical. Except for prominent iris processes in one child (patient A-II-6), gonioscopic examination did not reveal hyperpigmentation or angle maldevelopment. Interestingly, that same child had the greatest number of iris lesions. Visual acuity and iris motor function were normal in all children. No other ocular or skin hyperpigmentation was noted in any of the family members except for a hairy naevus on the thigh of patient B-II-6.

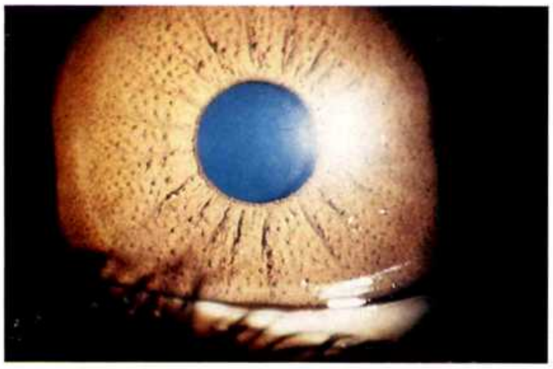

Fig. 7 *Iris of patient II-1 (family B) shows numerous elevations along the entire iris surface.*

The possible relationship to ocular hypertension is interesting. Two of the six children in family A (patients II-3 and II-6) had a raised intraocular pressure (24 mmHg OD, 22 mmHg OS; and 22 mmHg OD, 20 mmHg OS, respectively), on their initial examination. The conclusion that some of these pressures are abnormal is based on the distribution of applanation pressures in normal subjects aged 20–29, where the mean pressure plus two standard deviations above the mean yields an upper limit of normal of 20 mmHg.[8] One of the children (patient II-6) had a moderate degree of cup to disc asymmetry (0·25 versus 0·50). No visual field defects could be demonstrated by Goldmann perimetry. As a further investigation into these findings, home tonometry was performed on three of the children, showing abnormal pressure peaks in two of them (Table 2). The clinical significance of these findings is unknown, and periodic examinations are warranted because these children are considered to be at risk of developing glaucoma.

Detailed histological study of this disorder has not been undertaken. Some suggest that the iris excrescences may be due to irregular thickening of the anterior iris surface, with the remainder of the iris being normal.[1] They may also represent collections of large uveal melanocytes as seen in ocular melanosis.[9]

The relationship of iris melanosis to malignant melanoma is questionable. Incidences from 10 to 27% have been reported.[2,3] However, inspection of the actual case reports reveals that all such cases occurred in eyes with hyperpigmentation of the sclera, conjunctiva, or choroid, so that they had more generalised ocular melanosis, not the localised iris 'melanosis' as shown in our patients. In addition, these series do not specify the patient's race, nor do they make any distinction between congenital and acquired ocular melanosis, the latter of which is known to be associated with an increased incidence of malignant melanoma of the choroid in white patients.

The familial pattern in our two families suggests

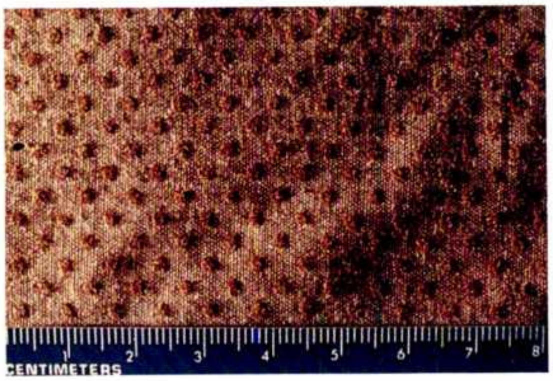

Fig. 8 *Piece of 'dotted-swiss' fabric with a surface pattern very similar to the iris in the described patients.*

the possibility of non-mendelian mechanisms (polygenic or multifactorial inheritance). The pedigree does not support an autosomal dominant pattern, and it would be unlikely for all children to be affected in a recessive pattern. There was no known parental consanguinity in either family.

The differential diagnosis of iris nodules is extensive, but two particular disorders deserve mention. The iris-naevus (Cogan-Reese) syndrome shares with iris melanosis its occurrence in young people and its association with raised intraocular pressure. However, the diffuse iris naevus in the iris-naevus syndrome can easily be distinguished from the discrete excrescences in iris melanosis. In addition the iris-naevus syndrome is unilateral and is associated with peripheral anterior synechiae and heterochromia, unlike iris melanosis. Neurofibromatosis (von Recklinghausen's disease) is another cause of bilateral iris nodules and congenital glaucoma, but the nodules tend to be larger than those in iris melanosis. Furthermore, the cutaneous, the central nervous system, and the systemic manifestations of neurofibromatosis serve to distinguish this condition from iris melanosis.

Finally, the term 'melanosis' refers to abnormally dark pigmentation of a specific tissue. The condition we are describing does not produce hyperpigmentation per se. Instead, the irides are characterised by discrete, round elevations on their anterior surfaces, which have previously been called mamillations. We therefore suggest another, possibly more descriptive name for this condition, such as 'dotted-swiss iris' (Fig. 8).

To our knowledge these are the first two families reported with more than one member having iris melanosis. This is also the first demonstration of a possible relationship to ocular hypertension. Further follow-up of intraocular pressures, visual fields, and optic discs will be necessary for a better understanding of the natural history of this condition.

We thank Kathleen Louden for editorial assistance and Linda Warren for her illustrations.

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Atypical band keratopathy following long-term pilocarpine treatment

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SUMMARY Two patients with an atypical form of band keratopathy following long-term pilocarpine treatment are described. The keratopathy is thought to have resulted from the presence of the preservative phenylmercuric nitrate in the pilocarpine drops. Symptoms of reduced acuity, visual haloes, and recurrent epithelial erosions were relieved by removal of the opacities.

In 1971 Kennedy *et al.*[1] drew attention to a form of band keratopathy occurring in glaucoma patients on miotics. The keratopathy was thought to result from exposure to phenylmercuric nitrate, the preservative agent in the drops used.[2] More recently Kenyon *et al.*[3] wrote that 'instillation of mercury-containing eye drops, as in glaucoma and dry-eye states, has some circumstantial relationship to the development of band keratopathy in some patients'. This paper records two cases of band keratopathy following long-term use of pilocarpine drops containing phenylmercuric nitrate.

Case reports

CASE 1

This patient initially attended in 1955 when aged 31. She complained of intermittent visual haloes associated with ocular pain. Visual acuities were normal, but the anterior chambers were shallow, with narrow angles on gonioscopy. Intraocular pressures and optic discs were normal, as were the other results of the ophthalmic examination. A diagnosis of intermittent angle closure glaucoma was made and treatment started with pilocarpine 0·5% drops twice daily to both eyes. The patient remained on this treatment without new symptoms or signs until 1982, a period of 27 years.

In 1982 she reported having blurred vision when looking towards bright lights, and she was found to have a faint opacity in the right cornea, inferonasal to the visual axis, at the level of the superficial stroma. An isolated crystalline deposit was in the inferonasal quadrant of the left cornea. Visual acuities were normal. During the next two years the corneal opacity increased in size and density in the right eye and a similar opacity appeared on the left. Serum calcium was normal.

The patient underwent bilateral laser iridotomy in 1984. During the following months she made a number of unscheduled visits to hospital complaining of haloes but each time had normal or minimally raised intraocular pressures and no corneal oedema. In addition the right acuity was now reduced, varying between 6/6 and 6/12 at different visits. There was quite marked granular yellow-brown discolouration of the cornea, maximal in the subepithelial zone, in a band shaped distribution (Fig. 1). Slit-lamp examina-

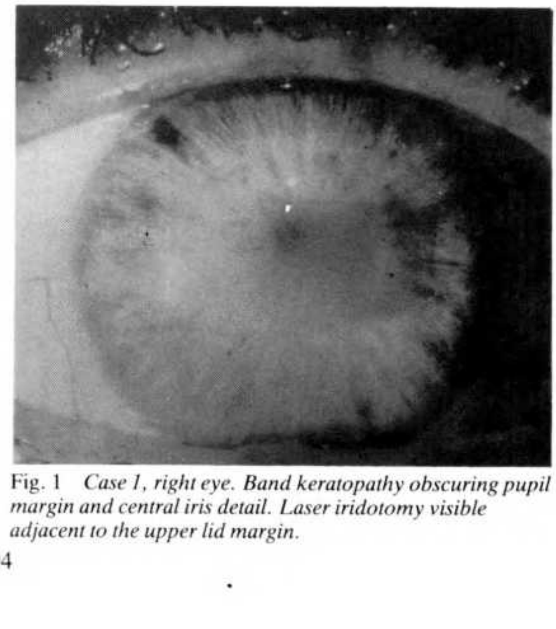

Fig. 1 *Case 1, right eye. Band keratopathy obscuring pupil margin and central iris detail. Laser iridotomy visible adjacent to the upper lid margin.*

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tion did not identify any associated changes in the anterior lens capsule of either eye.

The band keratopathy was removed under local anaesthesia in May 1985 with 0·37% edetic acid (EDTA) solution. The corneal epithelium healed without complication, acuity was restored to 6/5, and the visual haloes ceased. Changes in the left eye have not so far warranted surgical treatment.

CASE 2

This man was found to have primary open-angle glaucoma in 1958 and was treated with topical pilocarpine 0·5% three times daily and adrenaline 2% once daily. In 1963 faint opacities were noted in the nasal part of both corneas not extending to the limbus. During the following four years the opacities increased in density and occupied an increasing area of nasal and inferior cornea.

Because of impairment of visual acuity and recurrent episodes of irritation, the band keratopathy was removed from each eye by superficial keratectomy in 1967. The corneal changes recurred and required further intervention over succeeding years to maintain clarity of the visual axis or remove flakes of calcific material causing epithelial erosions. Throughout this period the patient used pilocarpine drops 0·5 or 1% three times a day in addition to other glaucoma treatments including adrenaline, adrenaline with guanethidine, dipivalyl adrenaline, and timolol. The serum calcium was normal.

Since 1984 argon laser trabeculoplasty and bilateral trabeculectomy have been required to control the intraocular pressure. At the most recent follow-up some pigment stippling of the anterior lens capsule was noted in each eye, though this was not associated with any generalised discolouration of the lens. Corrected visual acuities were right 6/12, left 6/9, with upper and lower arcuate field loss in both eyes.

Discussion

Band keratopathy is commonly seen in association either with a variety of other eye conditions, including uveitis, absolute glaucoma, and phthisis, or with systemic hypercalcaemia.[3 4] These causes are unlikely in the patients reported here; band keratopathy would be unusual in controlled glaucoma with good vision, and both patients were normocalcaemic. Primary (or idiopathic) band keratopathy[5] is another possibility. As neither patient gave a family history of corneal disease, considered important in diagnosis by Duke-Elder and Leigh,[4] this must also be considered unlikely.

The reported cases do, however, show features of the atypical form of band keratopathy initially described by Charney[6] and later by Kennedy *et al.*[1] The latter authors reported on 18 well controlled glaucoma patients who developed fine granular opacities in the lower central and nasal parts of the cornea. This band keratopathy was considered atypical because it began centrally and gradually extended towards the corneal periphery rather than starting at the limbus and extending centrally, as is more usual.[4] All affected patients were using miotics. In patients using miotics in only one eye the band keratopathy was restricted to the treated eye.

A further publication[2] contained a detailed analysis of the constituents of pilocarpine drops used by a total of 48 patients with the atypical band keratopathy. It transpired that all affected individuals used pilocarpine made by one manufacturer, which differed from other brands available in containing phenylmercuric nitrate as a preservative agent. It was concluded that the keratopathy resulted from the use of pilocarpine drops containing phenylmercuric nitrate, though no precise explanation of the mechanism was possible.

Both our patients were treated with pilocarpine preserved with phenylmercuric nitrate for many years, though this agent was not used in pilocarpine made at Moorfields Eye Hospital after the mid 1970s. Interestingly, both patients continued to develop corneal opacities after exposure to phenylmercuric nitrate ceased. This suggests either that phenylmercuric nitrate continues to predispose to development of band keratopathy after it has been discontinued or that another, as yet unidentified, factor is involved.

The theory that phenylmercuric nitrate has a significant role in development of the band keratopathy is supported by other reports of corneal opacification following exposure to both elemental mercury and phenylmercuric nitrate. Band keratopathy was reported in a barometer maker by Nettleship[5] and in thermometer makers examined by Atkinson[7] and Burn.[8] These occupations involved exposure to mercury vapour. Abrams, in his study of iatrogenic mercurialentis published in 1963,[9] reported band keratopathy in five patients treated with miotics containing phenylmercuric nitrate. Two of these patients had unexplained band keratopathy without signs of mercurialentis. Corneal changes in the other three cases could be explained by absolute glaucoma.

Neither patient reported on here was considered to show signs of mercurialentis, the grey-brown or yellow discolouration of the anterior lens capsule which may follow exposure to mercury or phenylmercuric nitrate.[7-10] The pigment deposits on the anterior lens capsule of case 2 were thought to be compatible with pigment release in the anterior segment after bilateral drainage surgery. Grant[10] noted that the report by Kennedy *et al.*[1] associating atypical band keratopathy with phenylmercuric nitrate made little mention of lens changes. In the same way relatively few of the reported patients with mercurialentis following use of drops containing phenylmercuric nitrate had corneal signs.[9] It therefore seems that the corneal and lens changes appear more often in isolation than together.

Reported symptoms of the atypical band keratopathy[1 2 4] include visual disturbance, photophobia, lacrimation, and irritation, the last three when erosion of the overlying epithelium occurs. Our first patient also suffered visual haloes caused by the granular opacity in the cornea. When the band keratopathy gives rise to symptoms, removal with edetic acid solution, as described by Grant,[11] is effective. The procedure can be repeated in the event of recurrence.

While no longer used in pilocarpine, phenylmercuric nitrate is still present in some drops prescribed for glaucoma and antibiotic preparations. The link should be borne in mind when patients develop band keratopathy during long-term topical treatment.

We thank Mr P Fells for allowing us to report a patient under his care (case 1) and the Departments of Medical Illustration at Moorfields Eye Hospital and St Thomas's Hospital, which respectively took and prepared the photograph for publication.

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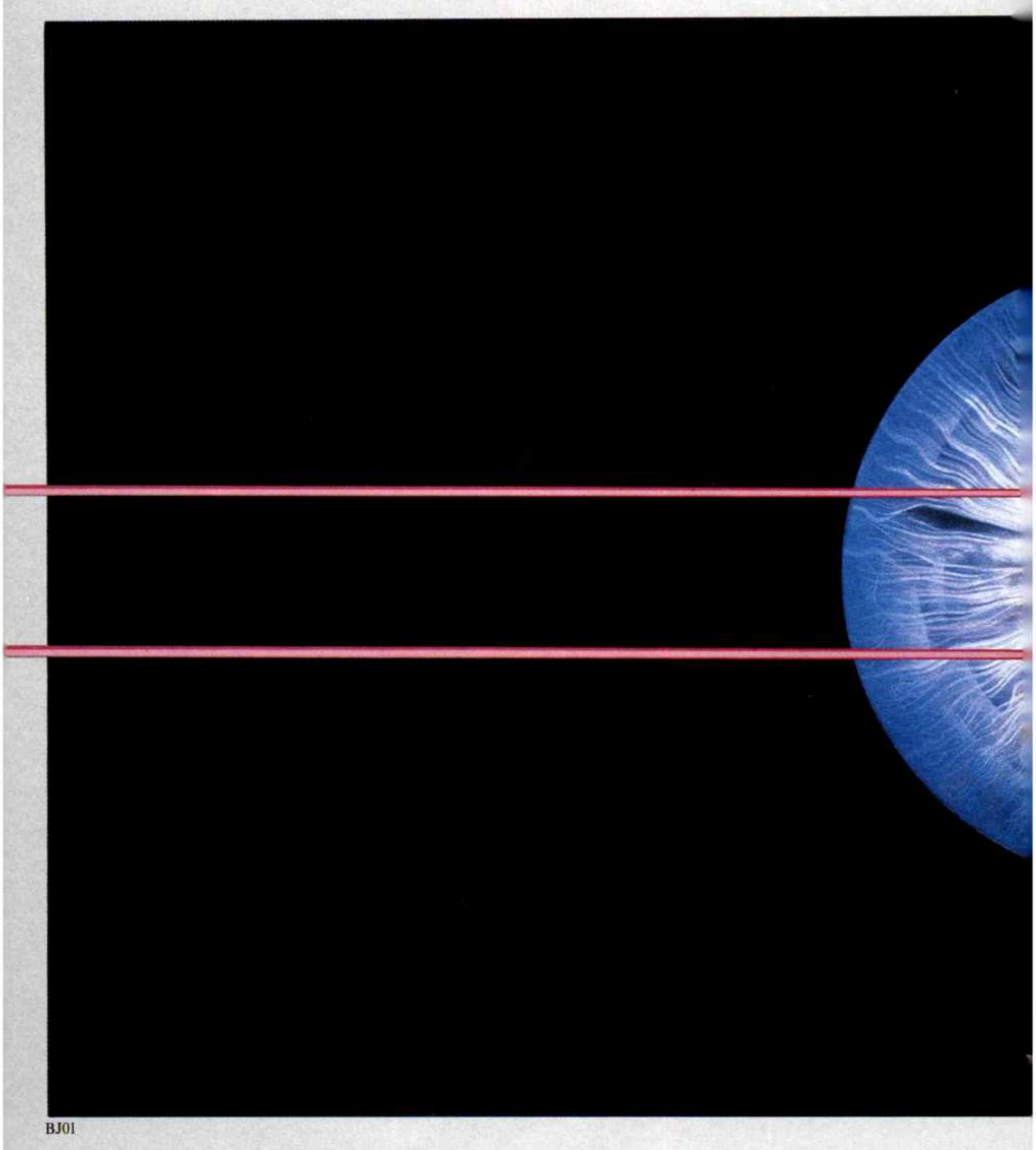

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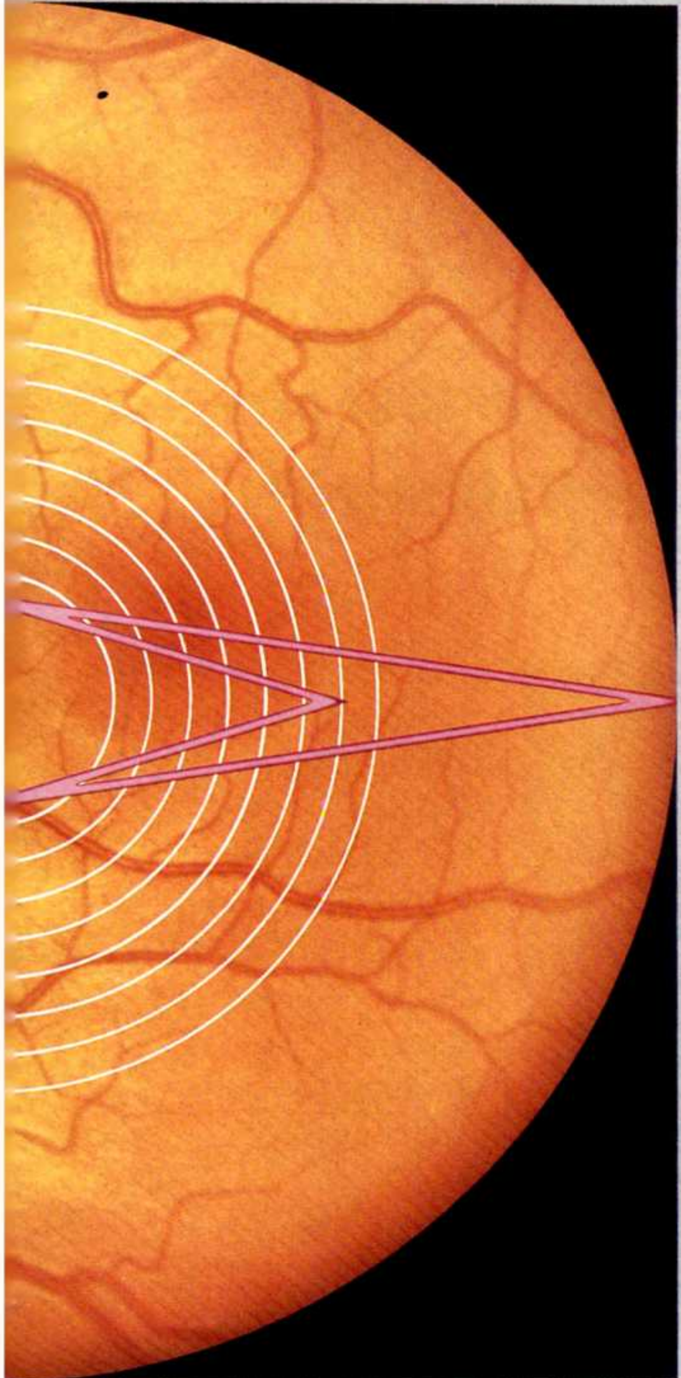

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British Journal of Ophthalmology, 1989, **73**, 297–302

Fundus changes in (type II) mesangiocapillary glomerulonephritis simulating drusen: a histopathological report

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SUMMARY We report for the first time to our knowledge the histopathological findings in the eye of a patient with type II mesangiocapillary glomerulonephritis (dense deposit disease) in which a deposit of material morphologically very similar to that which is pathognomonic for the disease in the kidney was demonstrated in Bruch's membrane. The nature of the deposit in the renal lesion is unknown but is considered to represent a structural alteration secondary to a reaction with anticomplement antibody. Clinically the fundus appearance resembled that seen in drusen.

Glomerulonephritis can be classified according to the histopathological appearances. In type II mesangiocapillary (MCGN type II) glomerulonephritis a deposit, characteristically electron dense on electron microscopy, is seen in the glomerular capillary basement membranes. We report here the clinical case and ocular histopathological findings in a patient with MCGN type II in whom a deposit of abnormal material in the choroid and Bruch's membrane similar to that demonstrated in the glomerulus was present. The choroid and the kidney have anatomical similarities in that they both have a large capillary bed made up of fenestrated vessels, and we suggest that the two sites may be affected by similar disease processes.

Case report

CLINICAL HISTORY

An 18-year-old male patient presented in March 1981 with a two-week history of malaise, leg cramps, ankle swelling, and nocturia. On renal biopsy his nephrotic syndrome was found to be due to type II mesangiocapillary glomerulonephritis. He was initially treated with diuretics, a low salt diet, and hydrallazine to control his blood pressure, which was raised to 150/100 mmHg at presentation His renal function, however, continued to deteriorate, and in July he was started on plasmapheresis and immunosuppressive treatment. Having been normotensive since his initial presentation he became hypertensive in September with a blood pressure of 180/120 mmHg supine, 120/100 mmHg erect. The blood pressure was controlled within a few days with prazosin and metoprolol. However, during that time he complained of blurred vision and was found to have corrected visual acuities of 6/24 in each eye. The anterior segments were normal. He had bilateral papilloedema, macular oedema, and scattered flame-shaped haemorrhages. Over the next month the vision in the right eye deteriorated to hand movements only, while in the left it improved to 6/12 with gradual resolution of the signs. At about this time he was started on haemodialysis.

On 9 July 1982 he returned to the eye department with a complaint of pain in the right eye which occurred only while on dialysis. In the right eye there was no perception of light, an afferent pupil defect, corneal oedema, and an intraocular pressure of 52 mmHg. The left eye had a visual acuity of 6/9, with no fundus abnormalities. The patient was treated with topical steroids, atropine 1% and timolol 0·5%, but he continued to complain of severe intermittent pain while on dialysis. On 27 July when seen again he was found to have a massive exudative bullous retinal detachment. The intraocular pressure remained raised, and he was admitted to hospital for attempted

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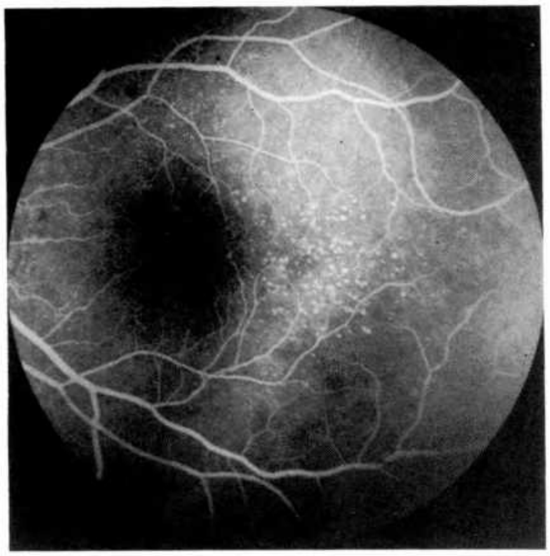

Fig. 1 *Fluorescein angiogram of left eye showing multiple hyperfluorescent foci with the characteristics of drusen.*

medical control with the addition of acetazolamide. This failed, as did two retrobulbar injections of alcohol, to alleviate his pain, and the right eye was enucleated on 10 August 1982. Fluorescein angiograms of the left eye on 6 September showed no disturbance of choroidal or retinal circulation. Although the fundus appeared normal, there were numerous hyperfluorescent discrete foci at the posterior pole and concentrated in the perifoveal area (Fig. 1), fluorescing early in the angiogram, and becoming more intensely fluorescent throughout. These are the angiographic appearances of drusen.

The patient had remained well on continuing renal dialysis with no change in the appearance of the left eye, but he collapsed and died on 9 April 1983. Necropsy revealed no other cause of death and it was concluded that he had had a cardiac arrest or arrhythmia. Examination of the kidneys yielded no additional information. The left eye was not obtained for examination.

RENAL BIOPSY PATHOLOGY

Light microscopy. There were eleven glomeruli in the biopsy. All the tufts showed the characteristic appearances of mesangiocapillary glomerulonephritis with marked mesangial increase, involving particularly the matrix, but also some cellular proliferation. Long stretches of the capillary basement membrane stained highly periodic acid Schiff (PAS)-positive and thickened. Five of the glomeruli showed large epithelial crescents.

Immunofluorescence microscopy showed large amounts of C3 and IgM in capillary walls, the latter in focal and segmental distribution. Little positive fluorescence was seen in the mesangium. C3 and C4 were present also in some tubular basement membranes.

Transmission electron microscopy showed the presence of an electron dense deposit throughout the glomerular capillary basement membrane, thickening the membrane irregularly in some places (Fig. 2).

The appearances were those characteristic of type II mesangiocapillary glomerulonephritis (dense deposit disease).

EYE PATHOLOGY

Macroscopic examination and preparation of tissue. The right globe was immediately fixed in 10% formol saline. The eye was opened horizontally, revealing a total retinal detachment with a subretinal coagulum.

The pupil-optic nerve block was processed through paraffin, and sections were examined after staining with the following: haematoxylin and eosin, periodic acid Schiff, Bodian, Loyez, and Martius scarlet blue. Immunoperoxidase staining for IgG, IgM, kappa chain, lambda chain, C3 and C4 was also undertaken.

Tissue from the calottes was prepared for transmission electron microscopy.

Sections of 1 to 2 μm were cut and stained with toluidine blue for orientation by light microscopy. Sections from selected blocks were cut at 50 to 80 nm, stained with uranyl acetate and lead citrate, and examined and photographed with a Phillips 301 electron microscope.

Light microscopic examination. The corneal epithelium was thinned, with intraepithelial oedema and some bullous separation. The drainage angle was closed by an extensive neovascular membrane over the iris surface, with considerable ectropion uveae and a mild mixed inflammatory cell infiltrate in the iris. The ciliary processes were atrophic, with PAS-positive deposit in the basement membrane and the stroma of the processes.

The choroid was thinned, but the vessels in all layers were patent (Fig. 3). There was an extensive deposit of PAS-positive material both in the walls of the choroidal blood vessels and in Bruch's membrane, which showed both linear thickening (Fig. 3) and focal deposition, resembling drusen; this was present throughout but most marked at the posterior pole. The deposit stained positively for fibrin with Martius scarlet blue, unlike typical drusen. No immunoglobulin or complement could be demonstrated in the deposits.

The retinal pigment epithelium showed some proliferation, with the formation of a cellular membrane inside the pigment epithelium. There was a

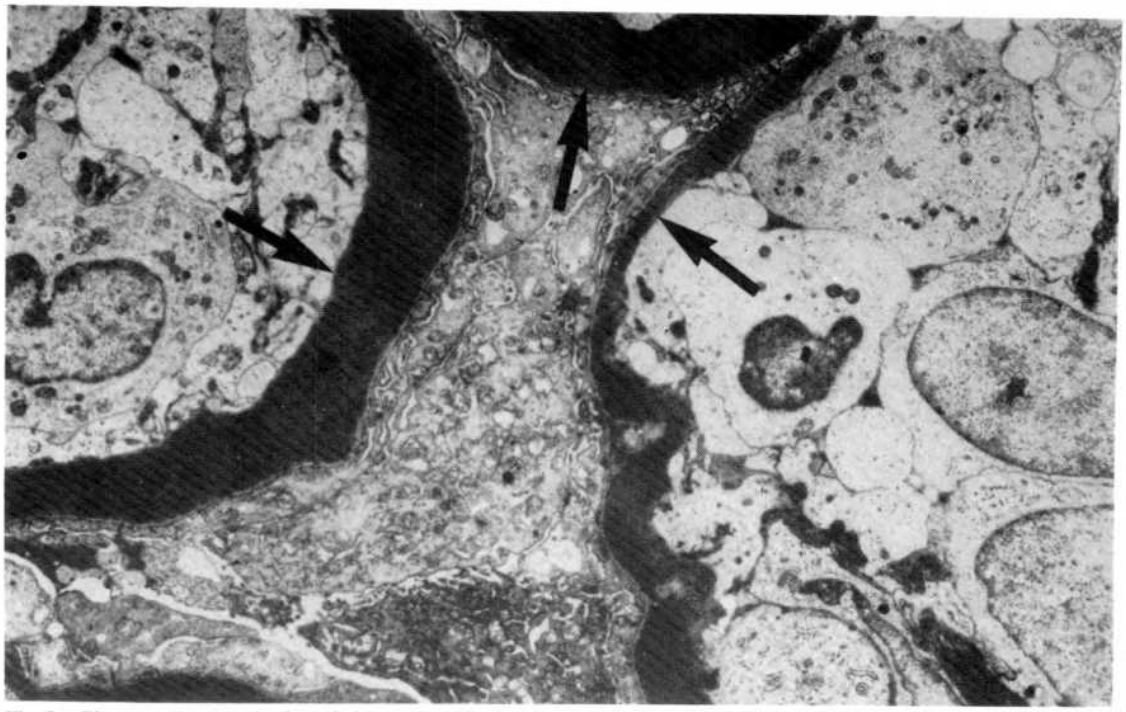

Fig. 2 *Electron micrograph of renal glomerulus. The basement membrane of the walls of three glomerular capillaries can be seen (arrows); the membrane varies in width and is abnormally electron dense. ×2000.*

total retinal detachment, with extensive recent and organising intraretinal haemorrhage. The retinal architecture was completely replaced by glial cells, and the subretinal space was filled with eosinophilic material showing cholesterol clefts and containing many pigment laden macrophages. Some of the retinal vessels, particularly at the periphery, showed thickening of their walls. There was an extensive fibrovascular preretinal membrane.

The optic nerve was markedly atrophic with very few nerve axons, and showed anterior demyelination. The posterior ciliary vessels were patent but fibrin was focally deposited in their walls.

Electron microscopy. It was confirmed that a deposit was present in the basement membrane of the ciliary epithelium (Fig. 4) and throughout the extent of the inner collagenous layer of Bruch's membrane, where it took two forms, being both linear and focal

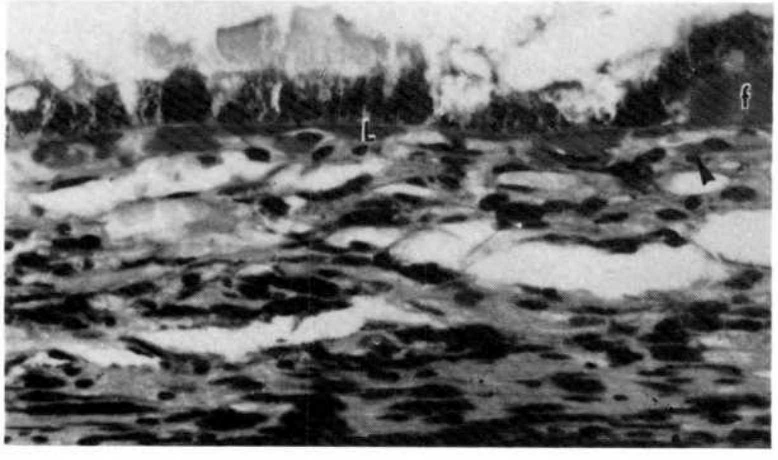

Fig. 3 *Choroid and Bruch's membrane showing both focal* (f) *and linear* (l) *thickening. Note that the vessels in all layers of the choroid are patent, but show some deposition of material in their walls (arrow). ×1000.*

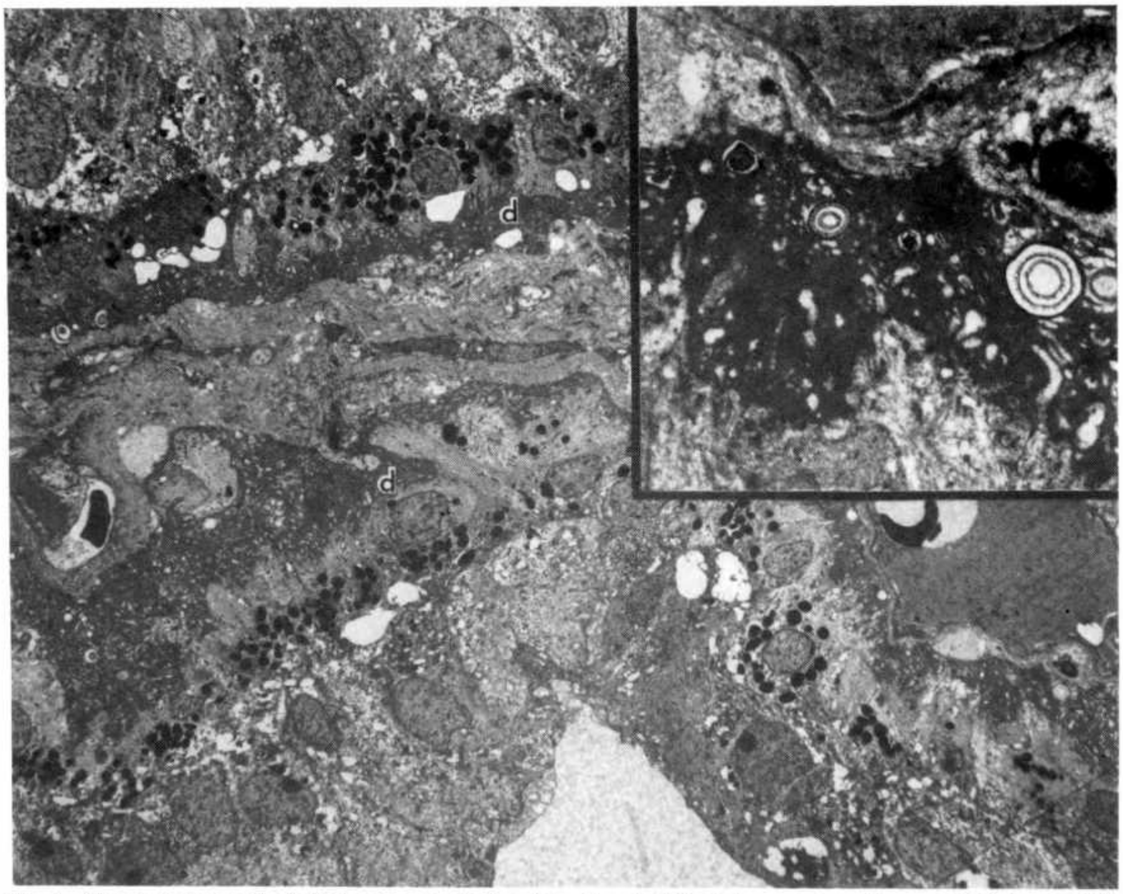

Fig. 4 *Electron micrograph of ciliary processes showing dense deposit* (d) *in the basement membrane.* ×*1500. Inset* ×*6000. Note also deposit in basement membrane of choriocapillaris.*

(Fig. 5). The deposit was present also in capillary basement membranes. The material was electron dense and amorphous, as in the kidney, though less densely staining.

Discussion

Type II mesangiocapillary glomerulonephritis is a relatively rare but well recognised condition. The histopathological hallmark is the presence of a linear electron dense deposit in the glomerular capillary basement membrane.[1] The pathogenesis is unknown, but there is evidence that an anticomplement antibody is implicated, and the serum complement is characteristically low. However, the situation is complex, and as yet there is no definite knowledge of the nature of the dense material in the basement membrane, though it has been suggested that it represents alteration in a glycoprotein of the basement membrane itself. Immunopathology often shows C3 almost alone in the capillary walls, as in this case.

In a previous experimental study of the choriocapillaris a comparison between the anatomy of the glomerulus and of the choriocapillaris/Bruch's membrane/retinal pigment epithelial complex has been drawn.[2] To our knowledge this is the first case to be reported of type II MCGN with clinical and histopathological evidence of ocular involvement similar to the glomerular lesion.

The results of previous studies of ocular pathology coexisting with glomerular disease are shown in Table 1.

In a mouse model of systemic lupus erythematosus (SLE)[3] the immunoglobulin deposits identified were found in the choroidal vessels, Bruch's membrane, and ciliary processes as well as in glomeruli, the choroid plexus, and the capillaries at the epidermal-dermal junction. A similar distribution of deposition of immune complexes is found in rat serum sickness.[4]

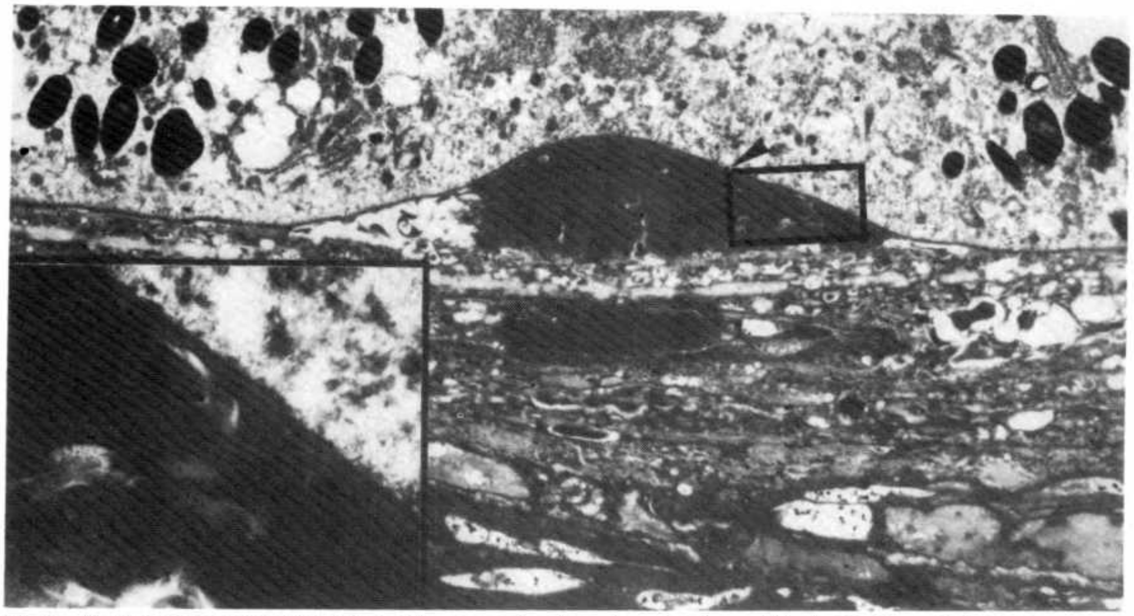

Fig. 5 *Electron micrograph of Bruch's membrane showing dense deposit in drusen-like distribution and also in the chorocapillaris (arrow) ×2730. Inset: at higher power the deposit is homogeneously dense. ×20 600.*

However, there are only two reports of deposition of immune complexes in human cases, one describing the post-mortem findings in a case of SLE in which the deposits were not detectable clinically,[5] and the other a case of Goodpasture's syndrome (anti-glomerular basement membrane disease) in which immune complexes were deposited in a uniform linear pattern due to an antigen/antibody reaction in the basement membrane.[6] Drusen-like deposits have been described clinically in a kappa chain monoclonal gammopathy[7] and occur in 21% of patients with SLE.[8]

We presume that in the case we report abnormal material, possibly of immune complex nature, has been derived from the blood, having escaped through damaged vessel walls. Aronson *et al.*[5] found in their patients with SLE, who were not hypertensive, that there was leakage of fluorescein from atypical drusen into the subretinal fluid under areas of localised retinal detachment.

We would suggest that abnormal deposits in Bruch's membrane and the choroid may be not infrequent in immunologically mediated renal disease, but that they remain unrecognised because the eyes have not been examined histologically.

The deposit in the eye did not stain for immunoglobulin or complement. However, the dense deposit typical of the lesion is not itself immunoglobin or complement but rather represents a structural alteration in extracellular tissue which may be a result of deposition of immunoglobin or complement. The immunoglobulin or complement may be only transiently associated with the basement membrane, which, however, remains morphologically changed. The failure to demonstrate immunoglobulin or complement in the ocular lesion in this case, and in

Table 1 *Summary of literature*

	Disease state	*Site of deposition*			
		Conjunctiva	*Ciliary body*	*Bruch's membrane*	*Choroidal vascular basement membrane*
Jampol *et al.*[6]	Goodpasture's disease	–	+	++	++
Pertschuk *et al.*[3]	Animal model: SLE	–	++	++	++
Peress *et al.*[4]	Animal model: rat, chronic serum sickness	–	++	–	–
Aronson *et al.*[5]	SLE	+	++	++	++
Nik *et al.*[7]	IgA-kappa chain monoclonal gammopathy (no histology)	–	–	+	–

the glomerular lesion in some other cases, may be related to the timing of the histological examination in relation to the onset or activity of the disease.

Our patient had a retinal venous occlusion and a retinal detachment, both attributable to accelerated hypertension. Retinal detachment is a well described complication of accelerated-phase hypertension, particularly in toxaemia of pregnancy.[9] The cause is thought to be massive exudation of fluid into the choroid with breakdown of the blood-eye barrier.[10] This has been demonstrated by fluorescein angiography in which dye is shown to leak out from the choroid into the subretinal fluid.[11 12] In all the reported cases of retinal detachment associated with renal failure the patients had marked hypertension.[13 14] The vascular changes in the choriocapillaris could be attributed to hypertension in this case,[15 16] but a deposit such as one described in the stroma of the choriocapillaris and Bruch's membrane has never been previously described. Additional evidence to support our belief that we are describing a new phenomenon is that we did not see typical infarcts of the pigment epithelium,[10] though these are not an invariable feature of accelerated hypertensive retinopathy.

Retinal venous occlusion may occur in patients on renal dialysis, probably as a result of raised intraocular pressure.[17 18] The relative hyperosmolality of the intraocular fluid after dialysis results in an influx of water into the eye under osmotic pressure, with a rise of intraocular pressure of up to 16 mmHg.[18] This phenomenon could also account for the pain of which this patient complained following episodes of dialysis.

This case demonstrates involvement of the choriocapillaris and Bruch's membrane and of the renal glomeruli in a similar morphological change; a clinical correlation with drusen-like spots in the fundus is also present. The choriocapillaris/Bruch's membrane/RPE complex has morphological similarities with the glomerulus. We suggest that both sites may be affected by similar disease processes and that the response of the choroid in renal disease merits further investigation.

We thank Professor W R Lee, University of Glasgow, for his advice and encouragement, and we are grateful to Dr A Lambie and Dr R J Winney, Medical Renal Unit, Royal Infirmary, Edinburgh, for permission to report this case

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Vitrectomy in aphakia: a simplified technique for fundus visualisation*

OSAMA M ASFOUR AND AYMAN NASSAR

From Benha University, Egypt

SUMMARY By using a small air bubble that fills about two thirds of the anterior chamber the erect image of the fundus of the aphakic human eye can be visualised clearly during vitrectomy, enabling the surgeon to operate without the need for vitrectomy lenses. The refractive power of the human aphakic eye is calculated here and the image site and size are presented.

During vitreous surgery surgeons use different types of vitrectomy lenses that are either fixed to the corneosclera or held by an assistant to provide a clear view of the fundus. In patients undergoing vitrectomy the removal of the crystalline lens is rather common. In this paper we revive a simple old optical principle that we hope will simplify and shorten the vitrectomy techniques in aphakia.

In our aphakic patients undergoing vitrectomy and in patients undergoing pars plana lensectomy and vitrectomy we were able to provide a clear view of the fundus during surgery simply by injecting through a limbal incision a small air bubble that fills one-half to two-thirds of the anterior chamber. Owing to the bubble's small size and to the minimal movement of the eye during surgery the back of the cornea was kept wet all the time, leading to perfect visibility during the whole procedure. This obviates the fogging effect caused by irregular wetting of the back of the cornea when the whole eye is filled with gas or air. Peripheral portions of the fundus were easily visualised by tilting the globe in the desired direction, the examination being aided by the superior position of the air bubble in the anterior chamber. The change in magnification owing to the relative peripheral corneal flattening is gradual and practically negligible.

Optics

In aphakia the refraction of the eye occurs at the anterior and posterior surfaces of the cornea and is 43·05 dioptres.[1] The equivalent refractive power of two separated optical surfaces can be given by the Gullstrand's equation:

$$F=D1+D2-D1\,D2{*}\,d/n,$$

where F is the total refractive power of the two surfaces, D1 and D2 are the refractive powers of the two surfaces, d is the distance between the two refracting elements (measured in metres), and n is the refractive index of the medium in between.[2] (The asterisk denotes multiplication.)

The optical power of the aphakic eye when ½ to ⅔ of anterior chamber volume is filled with air is nearly the same as when the whole eye is filled with air, that is, about −5·48 dioptres, owing to the relatively flat interface between the air bubble and aqueous or vitreous.

When the same refractive index is present on both sides of the lens, the nodal and principal points coincide.[3] And since in that situation the cornea is the only refractive system and is surrounded by air on

Table 1 *From 'Schematic eye'*[1]

Refractive index	
Cornea	1·376
Aqueous humor and vitreous body	1·336
Position	
Anterior surface of cornea	0
Posterior surface of cornea	0 5
Posterior surface of lens	7·2
Radius of curvature	
Anterior surface of cornea	7·7
Posterior surface of cornea	6·8
Posterior surface of lens	−6 0
Refracting power	
Anterior surface of cornea	48 83
Corneal system	43·05

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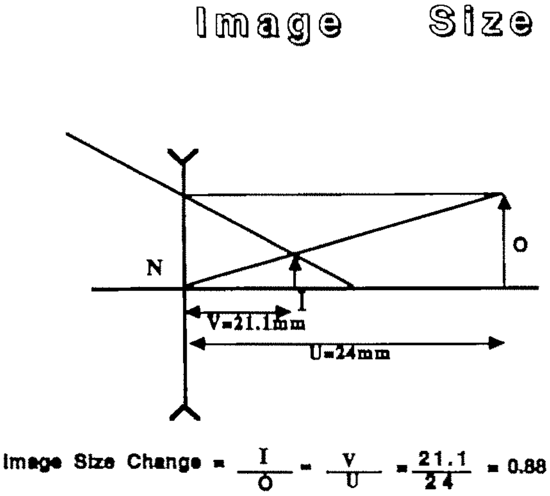

Fig. 1 *The image/object size ratio.*

either side, all measurements were calculated from the anterior corneal surface.

As regards the position of the image, it was found to be situated about 21·1 mm from the corneal surface, as calculated from the equation

$$D=1/U+1/V$$
$$V=1/[D-(1/U)],$$

where D is the refractive power of the cornea with air on both sides, and U and V are the corresponding retinal and image distances from the corneal surface.

The image/object size ratio as calculated from the following equation is about 0·88:

$$\text{Image/object}=I/O=V/U=21{\cdot}1/24=0{\cdot}88,$$

where O and I are the corresponding object and image sizes, and V and U are the corresponding image and retinal distances from the surface of the cornea.

This means that we get a slightly reduced virtual image of the retina that is situated inside the eye about 3 mm in front of an emmetropic retina.

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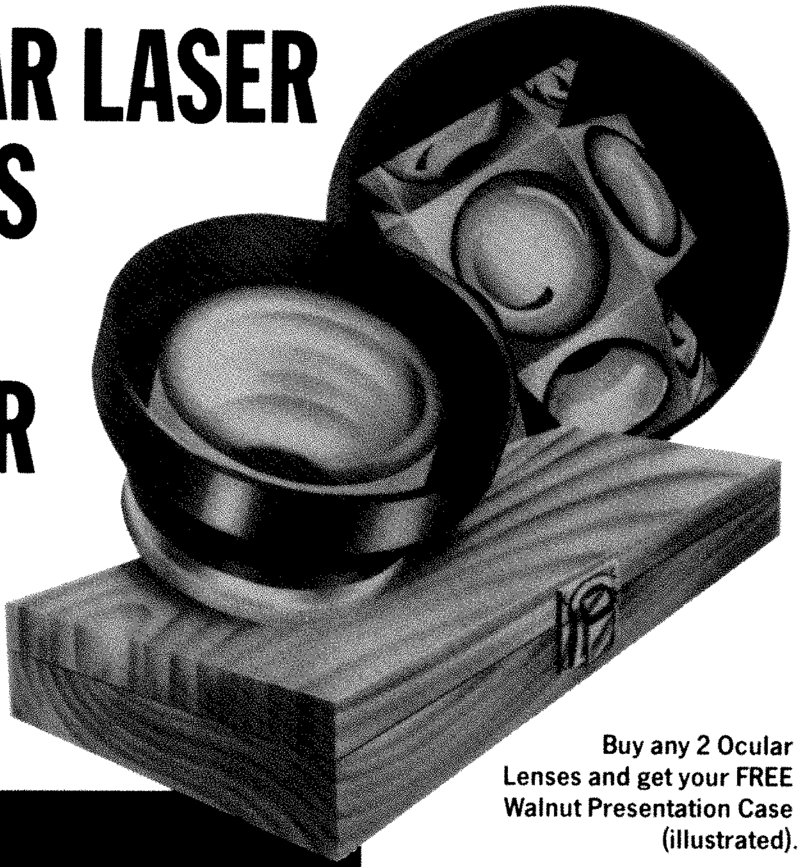

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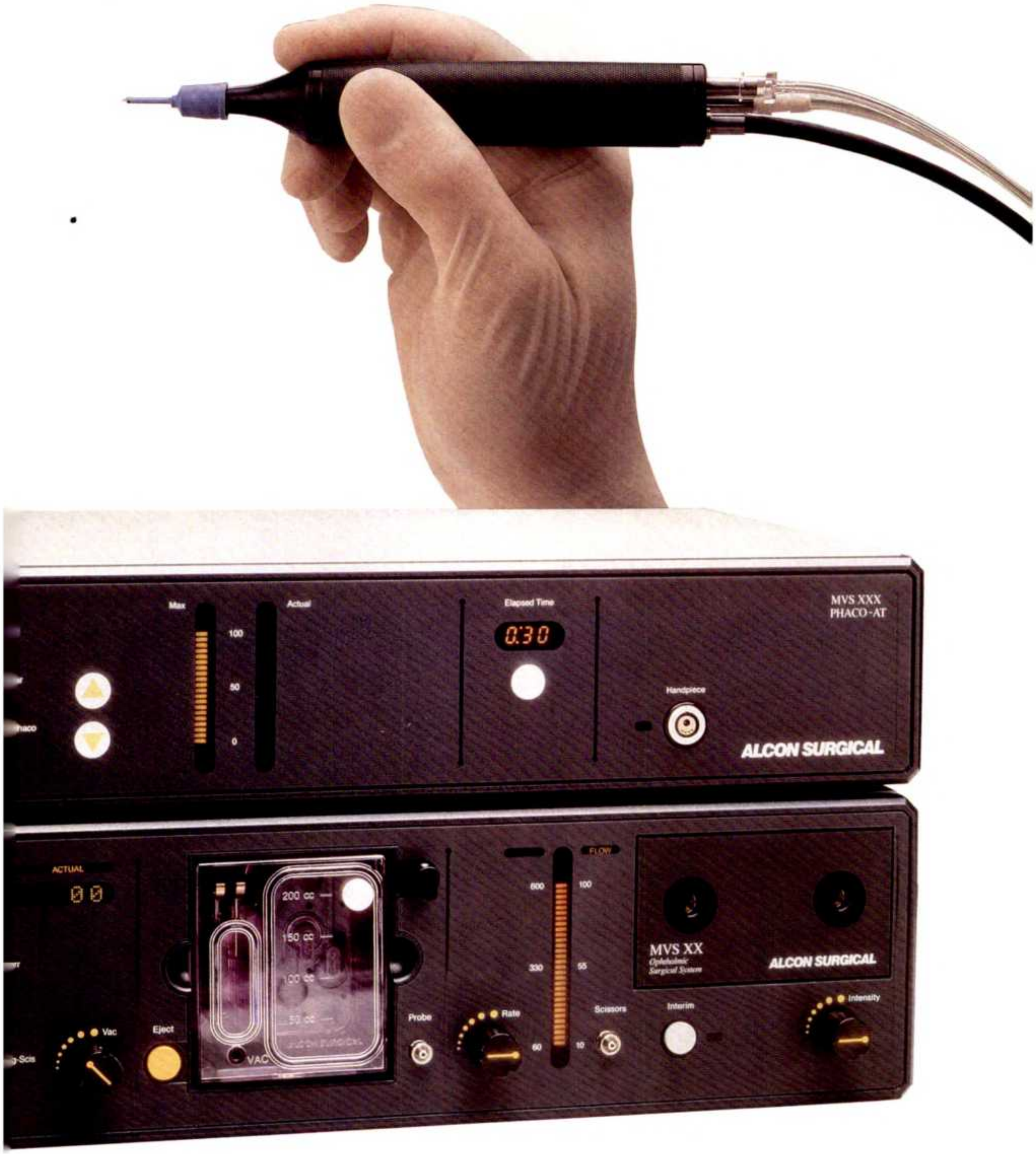

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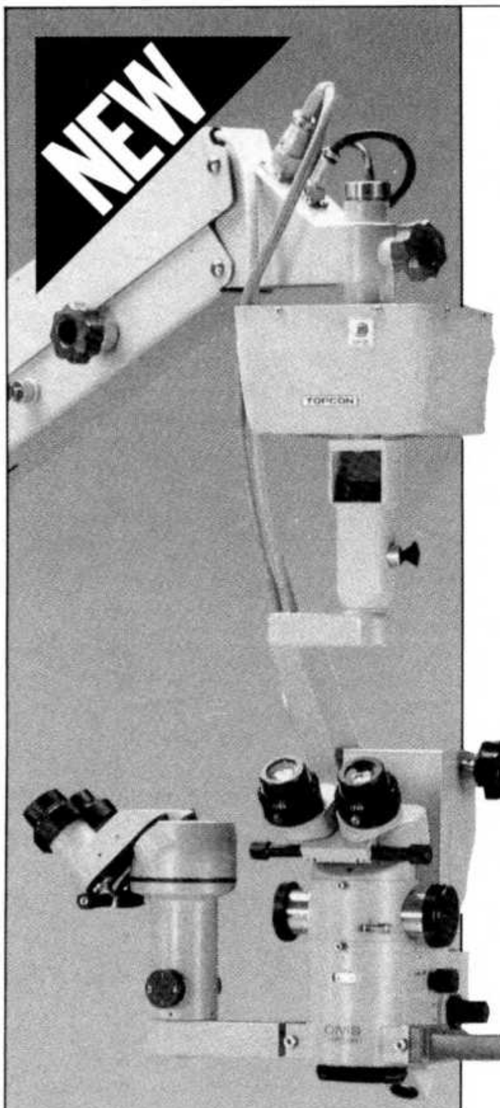

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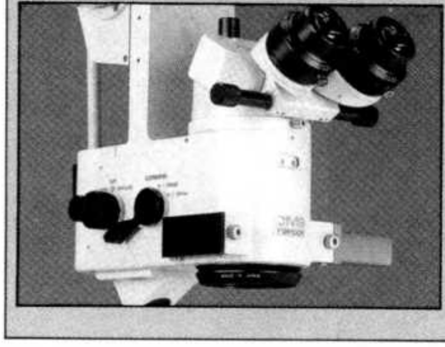

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British Journal of Ophthalmology, 1989, 73, 305–308

Case reports

Acquired Brown's syndrome associated with Hurler-Scheie's syndrome

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SUMMARY A 5-year-old Caucasian girl with known Hurler-Scheie's syndrome (mucopolysaccharidosis) developed a right Brown's syndrome while under orthoptic review. There was no evidence of trauma or inflammation of the superior oblique tendon, trochlea, or surrounding tissues. The Brown's syndrome in this case may be due to shortening of the superior oblique tendon, associated with the shortening of long tendons of the arms and feet, which is common in Hurler-Scheie's syndrome.

Hurler-Scheie's syndrome is an autosomal recessive mucopolysaccharidosis which results in reduced activity of the enzyme α-L-iduronidase with subsequent accumulation in the tissues of heparan and dermatan sulphate. The syndrome represents a spectrum of disease, patients with the more severe, rapidly progressive disease being classified as Hurler's syndrome (mucopolysaccharidosis I-M) and those less severely affected as Scheie's syndrome (mucopolysaccharidosis I-S).[1]

The clinical features of Hurler-Scheie's syndrome are presented in Table 1.

Brown's syndrome is due to a mechanical limitation of movement of the superior oblique tendon, which results in a limitation of elevation in adduction. The condition may be congenital or acquired. Most cases of acquired Brown's syndrome are due to trauma or inflammation of the superior oblique tendon/trochlea complex. So far no cases have been described of an acquired Brown's syndrome in association with Hurler-Scheie's syndrome.

Case report

The patient, a 5-year-old girl with known Scheie's syndrome, was first referred to the Ophthalmic Department in 1985 having developed bilateral corneal clouding (her younger brother has Hurler's syndrome). General examination revealed abnormal facies (Fig. 1), coarse hair, and contracture of fingers (Fig. 2), elbows, and hips. She was of normal height and intelligence; orthoptic assessment showed her to be orthophoric, with unaided vision of 6/9 right 6/9 left. Slit-lamp biomicroscopy confirmed the presence of mild corneal clouding (Fig. 3), but there were no other ocular signs of Scheie's syndrome.

When she attended some eight months later her mother reported that she had recently noticed the development of a convergent squint. On examination the patient had an esotropia measuring 20 prism dioptres base out both for near and distance. Wearing the full hypermetropic correction (OD +4·0, OS +3·50) reduced the angle of deviation to 8 prism dioptres base out for near and distance.

There was no change in her squint or visual acuity

Table 1 *Clinical features of Hurler-Scheie's syndrome*

Non-ocular features[2]
1. Abnormal facies, enlarged skull, thickened lips, prominent forehead, coarse hair, abnormally low ears
2. Contracture of hips, knees, elbows, and fingers
3. Hepatosplenomegaly
4. Diastasis recti, umbilical hernia
5. Growth retardation
6. Mental retardation
7. Heart defects

Ocular features
1. Clouding of the cornea the opacities are stromal and Bowman's membrane is absent
2 Defective dark adaptation and ERG
3 Retinal degeneration
4. Optic atrophy
5 Ptosis
6 Strabismus (esotropia)
7 Glaucoma

Correspondence to J A Bradbury, FRCS Glas.

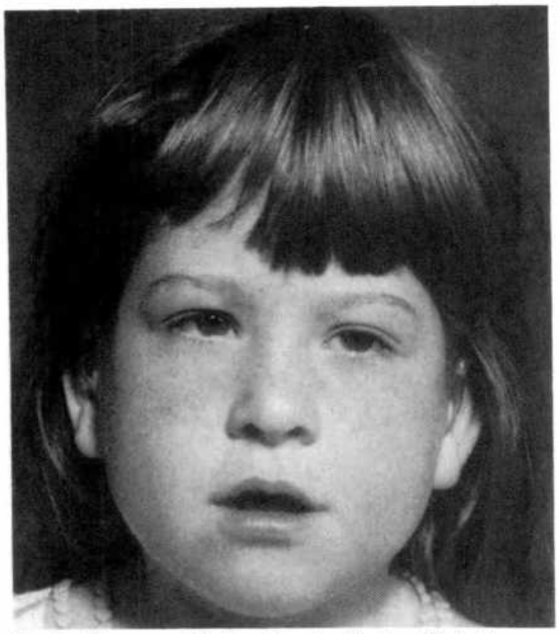


Fig. 1 *Five-year-old girl with typical facies of Scheie's syndrome.*

until December 1985, when her mother reported that she had 'started to look at her strangely'. There had been no change in her general health, she had complained of no pain, and there was no history of trauma. On examination there was no swelling or tenderness and no sign of trauma. Orthoptic examination (Fig. 4) revealed a marked limitation of the right eye on attempted laevo elevation with only a very slight limitation of the right eye in dextro elevation. She had also developed an 'A' esotropia which measured 20 prism dioptres base out for near and distance in the primary position, which increased to 35 prism dioptres base out in elevation and decreased to 4 prism dioptres base out in full depression. Unfortunately it was not possible to perform a forced duction test owing to poor patient cooperation.

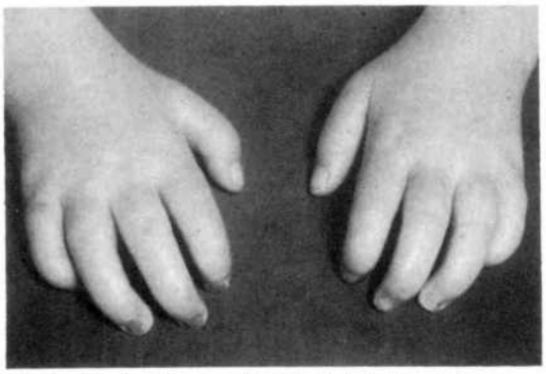


Fig. 2 *Hands of 5-year-old girl with Scheie's syndrome, showing contracture of fingers.*

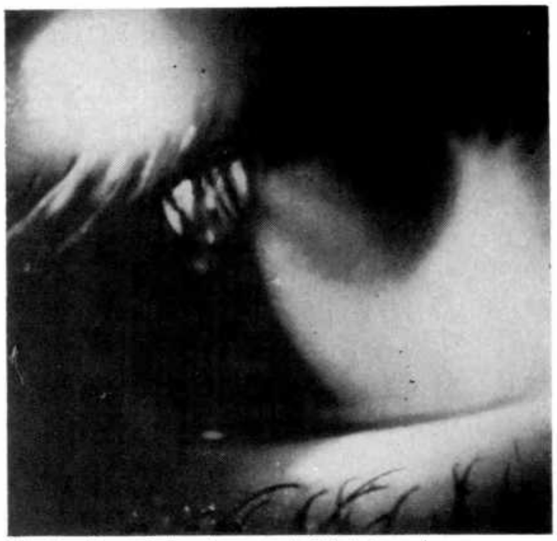


Fig. 3 *Corneal clouding seen in Scheie's syndrome.*

INVESTIGATION

A high resolution CT scan of both orbits was performed which showed no bony or soft tissue abnormality and no evidence of trauma or inflammation. A Hess chart (Fig. 5) confirmed the diagnosis of a right Brown's syndrome. This has remained constant since 1985.

Discussion

Most cases of acquired Brown's syndrome are due to trauma or inflammation of the superior oblique muscle, tendon, trochlea, or surrounding tissues.[3] It may also be caused by a tucking of the superior oblique tendon. Less well known causes include orbital metastasis.[4] In some non-traumatic cases nodules are thought to develop on the superior oblique tendon.[5] Such cases are often associated with rheumatoid arthritis or systemic lupus erythematosus and produce a palpable click on eye movement. In all cases the result is a mechanical limitation of the tendon/muscle complex producing defective upgaze in adduction.

Clinically the patient complains of diplopia in adduction and pain on movement, and may have tenderness over the trochlear region. On testing ocular movement there is reduced elevation in adduction. There may be a V exotropia or an A

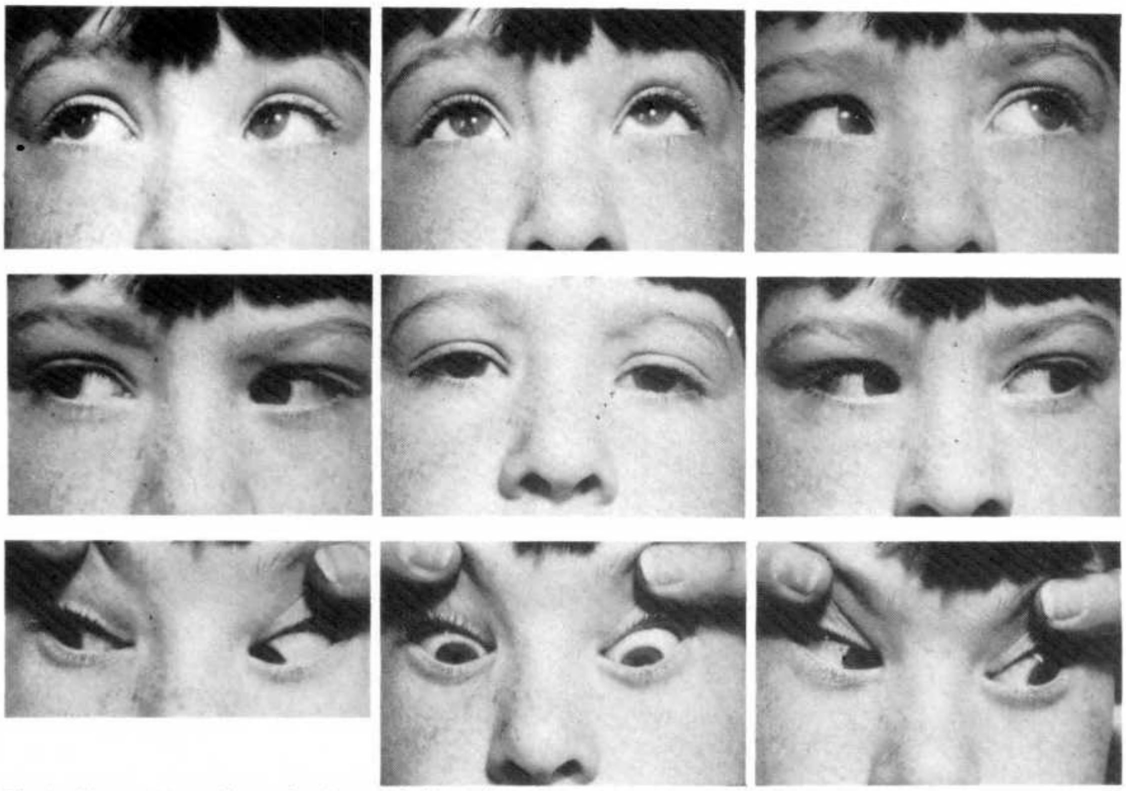
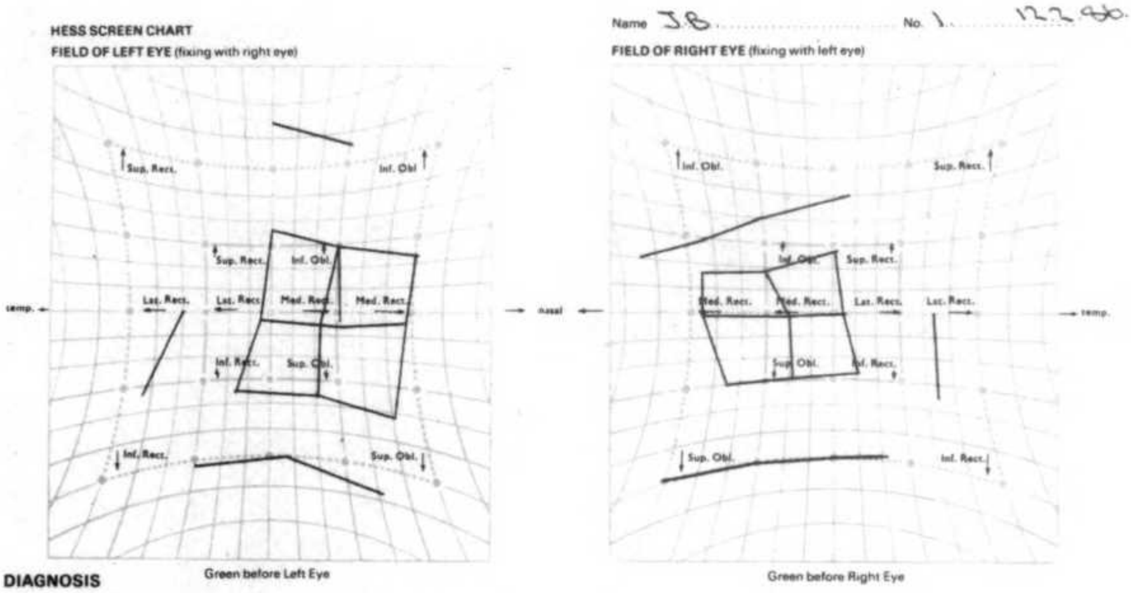


Fig. 4 *Nine positions of gaze showing a right Brown's syndrome.*



HESS SCREEN CHART

Name J.B. No. 1 12.2.80.

FIELD OF LEFT EYE (fixing with right eye)

FIELD OF RIGHT EYE (fixing with left eye)

DIAGNOSIS

Fig. 5 *Hess chart showing mechanical limitation of superior oblique tendon.*

esotropia.[5] A Hess chart will show the limitation to be mechanical; a traction test will confirm the mechanical limitation. This test would need to be done under general anaesthetic in children and is therefore impracticable, and in most cases only confirms what is already known

Inflammatory acquired Brown's syndrome responds well to local injection of steroids.[3] Traumatic cases generally respond poorly to steroids, but they may resolve spontaneously, if not, surgery may be needed. Both Parks[6] and Von Noorden[7] suggest a superior oblique tenotomy. A high proportion of these will develop a superior oblique palsy after surgery which can be managed with recession of either the ipsilateral inferior oblique or the contralateral inferior rectus muscle.

Acquired Brown's syndrome in a case of Hurler-Scheie's syndrome may be associated with the widespread shortening of tendons, especially the long tendons in the hands and feet. Possibly in this case the superior oblique tendon has become shortened, thereby producing a Brown's syndrome.

Brown's syndrome has not been noted previously in cases of Hurler-Scheie's syndrome.

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Branch retinal artery occlusion secondary to percutaneous transluminal coronary angioplasty

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SUMMARY We report on a patient suffering a branch retinal artery occlusion immediately following percutaneous transluminal coronary angioplasty. Balloon angioplasty may produce ocular embolic events consistent with previously reported neurological complaints.

Percutaneous transluminal coronary angioplasty (PTCA) was introduced in 1977.[1] It has successfully opened obstructed coronary arteries in properly selected patients.[1,2] Symptomatic, electrocardiographic, and angiographic improvement has been reported for up to three years after PTCA.[3,4]

The most frequent complications reported secondary to PTCA have been prolonged angina, myocardial infarction, and coronary occlusion.[5] We report the first case of a branch retinal artery occlusive event secondary to PTCA.

Case report

A 62-year-old white male suffered an uncomplicated inferior wall myocardial infarction in June 1987 and developed post-infarction angina. Two months later, on 12 August 1987, he underwent successful PTCA for a 90% stenosed circumflex artery. Immediately following the PTCA the patient complained of a visual deficit in the left eye. Ophthalmic examination showed 20/20 vision in each eye. A central 5° inferior absolute scotoma was detected in the left eye on tangent screen visual field testing. Ophthalmoscopic examination of the fundus revealed a superior temporal branch artery occlusion with retinal oedema (Fig. 1).

Discussion

Distal emboli to the heart and kidney have been reported following both coronary and renal artery balloon angioplasty.[5,6] In a study of 1500 patients following PTCA[5] 543 inhospital complications (21%) were reported. No ocular complications were mentioned. Four neurological complications were reported, including one cerebrovascular event and three transient ischaemic attacks.[5] These neurological complications and our patient's branch retinal artery occlusion show that balloon angioplasty may produce embolic events affecting tissues other than the target organ.

There are two mechanisms of embolisation potentially responsible for the branch retinal artery occlusion in our patient. First, atherosclerotic debris originating from pre-existing vascular lesions can result directly from catheterisation. This process

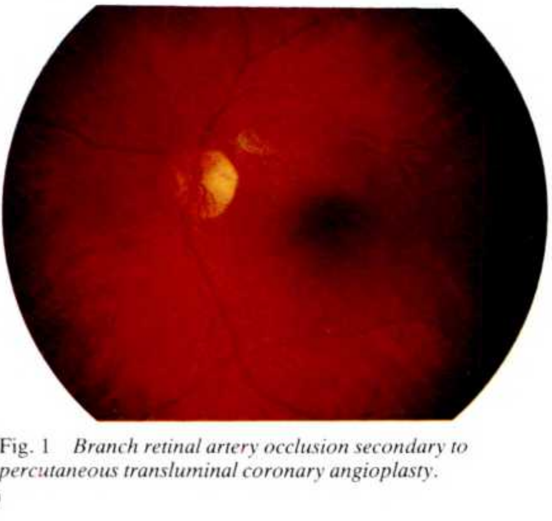

Fig. 1 *Branch retinal artery occlusion secondary to percutaneous transluminal coronary angioplasty.*

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usually results in cholesterol emboli. Secondly, a well recognised type of embolisation in any form of percutaneous cardiac catheterisation is the result of thrombus formation on the exchange guidewires. Embolisation occurs during the guidewire exchange process. It is impossible to determine which process is responsible for the vascular occlusive event without irrefutable evidence that the embolisation was due to cholesterol.

This work was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc.

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Sex linked juvenile retinoschisis with optic disc and peripheral retinal neovascularisation

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We wish to report a case of sex linked juvenile retinoschisis with optic disc and peripheral retinal neovascularisation. Both forms of neovascularisation resolved following panretinal photocoagulation. Optic disc neovascularisation has not been previously reported with this condition, though peripheral retinal vascular anomalies are well recognised.

Case report

The patient, a 24-year-old white male, first attended Moorfields Eye Hospital at the age of 7 years when referred with poor visual acuity at school eye testing. At that time his best corrected visual acuities were Snellen 6/36 in the right and 6/24 in the left eye. Slit-lamp biomicroscopic examination revealed bilateral foveal retinoschisis in a 'wheel-like' configuration (Fig. 1). Peripheral retinoschisis was absent. A general examination gave normal results. Low visual aids were dispensed when, at the age of 10 years, binocular distance visual acuity had deteriorated to 6/60 unaided.

There was a family history of sex linked retinoschisis, the patient's maternal grandfather having the condition. The mother and the twin sister of the patient were not, however, affected.

At the age of 20 the patient was re-examined after developing a symptomatic floater in the visual field of the right eye. His best corrected visual acuities at this time were 1/60 right and 6/36 left. Vitreous haemorrhage precluded examination of the fundus of the right eye. The right visual acuity improved to 6/36 as the vitreous haemorrhage cleared, but no source for the haemorrhage could be detected clinically at this stage. A further three vitreous haemorrhages occurred in the right eye during the next seven months, after which time fine, forward new vessels were detected at the right optic disc (Fig. 2) together with tortuosity of the peripheral retinal vessels. Flat new vessels in the retinal periphery were observed in the superonasal quadrant of the left eye.

Fluorescein angiography showed leakage of the dye from new vessels originating on the right optic disc (Fig. 3) and in the retinal periphery, together with areas of non-perfusion of the retinal capillary circulation in the periphery. There was leakage from peripheral retinal new vessels in the left eye, but no disc neovascularisation was present.

Panretinal photocoagulation of the right eye with argon blue-green laser was administered in three sessions over a five-month period, with regression of the neovascularisation within four months of the final treatment session (Fig. 4). A horizontal traction fold of the internal limiting membrane was noted to have formed accross the right macula (Fig. 4). Laser treatment was not administered to the left eye, and the peripheral new vessels underwent sheathing followed by spontaneous resolution.

Three years after panretinal photocoagulation the best attainable visual acuities were 6/36 right, and 6/60 left. Ophthalmoscopy showed bilateral cystoid macular oedema, peripheral retinoschisis, patchy sheathing of peripheral retinal vessels, many of which were straight and thin, peripheral retinal grey dots, and bilateral vitreous membranes. The right fundus also showed markedly pigmented scars due to the previous laser treatment (Fig. 4).

Blood tests, including syphilis serology and a glucose tolerance test, were normal. Electrodiagnostic tests showed no response to flash electroretinogram in either eye, but the electro-oculogram was 210% in the right and 200% in the left eye. B-scan ultrasonic examination showed detachment of the posterior vitreous face in both eyes, with intragel opacities.

Discussion

Peripheral vascular anomalies, considered by some authors often to pass undiagnosed, have been well described in sex linked juvenile retinoschisis. The peripheral retinal or schitic areas may be relatively avascular. Aberrant underdeveloped capillaries have

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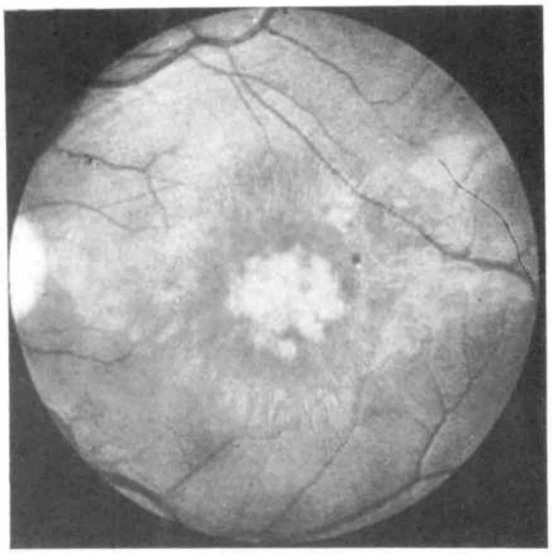

Fig. 1 *Left eye. Foveal retinoschisis in a 'wheel-like' configuration with microcysts and radial folds of the internal limiting membrane surrounding a central atrophic lesion.*

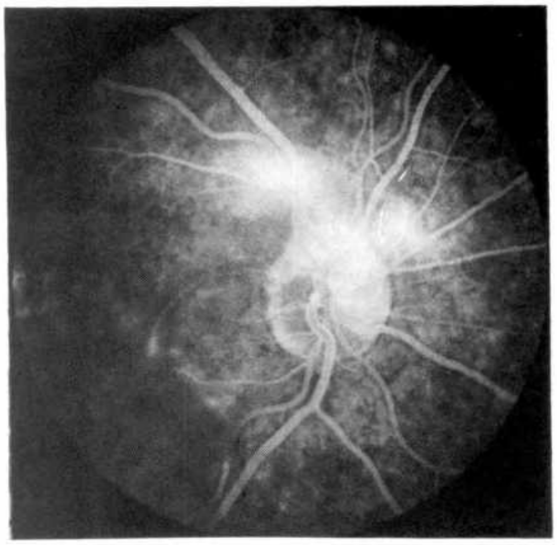

Fig. 3 *Fluorescein angiogram showing leakage of dye from new vessels at the right optic disc.*

been noted in retina central to such schitic areas, associated with greyish white dendritiform structures of vascular origin in the deeper layer of the peripheral retinal schisis itself.[1-4] Several authors have described arborisation (neovascularisation) of the peripheral retinal vasculature.[1,5-8] Some cases show slow circulation in one retinal quadrant or delayed filling of the central retinal artery.[3] The formation and coalescence of breaks in the inner layer of areas of peripheral retinoschisis may result in 'vitreous veils', which may contain veins and arterioles which are continuous with the retinal vasculature,[1,4] and some reports contain diagrams showing such vascularised veils attached to the optic disc.[8-10] Vitreous haemorrhage has been described, but unlike the condition in

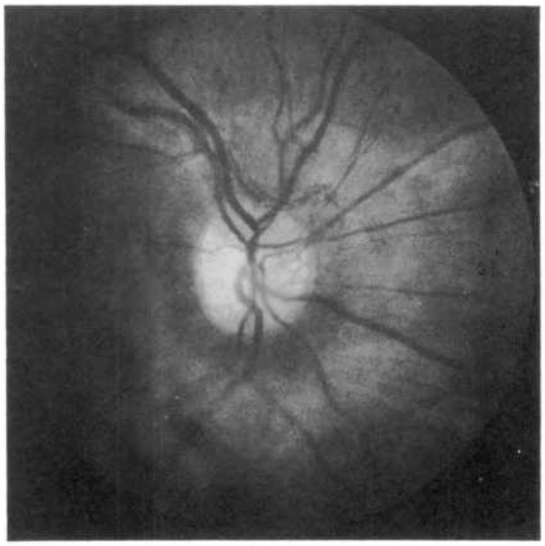

Fig. 2 *Forward new vessels at the right optic disc.*

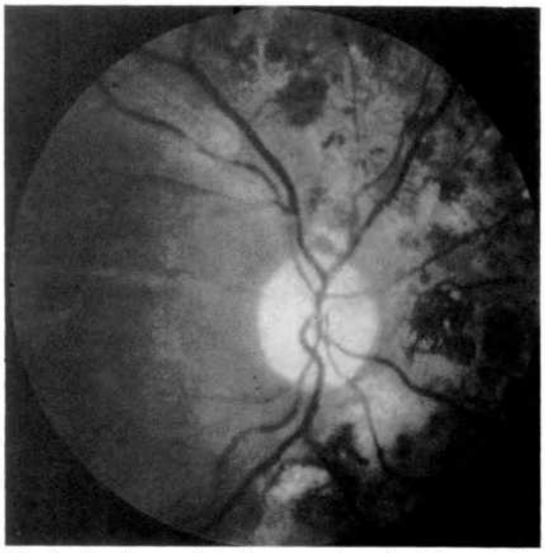

Fig. 4 *Total regression of new vessels at the right optic disc following panretinal photocoagulation. Horizontal traction fold of the internal limiting membrane across the right macula. Markedly pigmented scars due to previous laser treatment.*

this case, is most commonly due to rupture of vessels in the inner wall of areas of retinoschisis. Other vascular anomalies include temporally extending stretched vessels in the posterior pole, perivascular grey cuffing,[1] corkscrew and drumstick appearance of retinal vessels,[10] persistent hyaloid artery,[8] situs inversus vasculorum,[1] and an increased degree of branching of the retinal vessels on the surface of the optic disc.[1]

Peripheral retinal neovascularisation has been described so frequently in association with sex linked juvenile retinoschisis that it must certainly represent a feature of the 'disease' process. Optic disc neovascularisation has not, however, previously been described in association with this condition. The absence of any systemic disease known to be associated with retinal neovascularisation would suggest that the optic disc neovascularisation seen in this patient was a stage further than that of the peripheral neovascularisation frequently seen in this condition. That the underlying cause of the optic disc neovascularisation is retinal ischaemia is supported by the fluorescein angiographic findings and the response to panretinal photocoagulation. It is possible that the cause of the retinal ischaemia is related to the level of retinal splitting in the schitic areas. The level of splitting is very superficial, but sufficiently variable to include one branch of a retinal vessel in one layer while another branch may be seen in other layers.[3] Splitting at a deeper level, with the majority of vessels passing to the inner layer of schisis, may render those portions of the deeper layer relatively ischaemic, if they are not or are insufficiently supplied by the choroidal circulation This theory could not, however, explain the presence of avascularity of non-schitic areas of peripheral retina. A more plausible explanation may be that a retinal microangiopathy, which in extreme cases could produce sufficient retinal ischaemia to stimulate neovascularisation, is a feature of this condition and that its effects and appearance are modified by or contribute to the formation of schitic areas.

It is possible, but most improbable, that the optic disc neovascularisation is a vascularised 'vitreous veil' attached to the optic disc.[8-10] Such a proposition could explain fluorescein leakage by and vitreous haemorrhage from such vessels, but could not account for the regression of the vessels following photocoagulation. Nor is a mistake between the two likely on ophthalmoscopy or fluorescein angiography.

We thank Mr R K Blach for kindly giving his permission to report this patient under his care, and Mr Max Brown for his assistance with the photographs

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Leber's hereditary optic atrophy: further evidence for a defect of cyanide metabolism?*

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SUMMARY We studied one patient with Leber's optic atrophy (LOA) in the acute stage and 12 at the chronic stage of the disease, and measured the activity of rhodanese in white blood cells and the level of cyanide in whole blood. In the patient with acute disease the blood cyanide level was significantly increased at first. Treatment of this patient with cyanide antagonists reduced his cyanide level, but this was not accompanied by improvement in visual function. Rhodanese activity was normal in all patients, as were the blood cyanide levels in each of the 12 patients at the chronic stage of the disease. These findings suggest a temporary disturbance of cyanide metabolism during the acute phase of the disease in this family. The abnormal metabolic mechanism was not identified.

In 1965 Wilson[1] observed that in most cases of Leber's optic atrophy (LOA) the severity of the disease could be related to tobacco smoking. Because tobacco is the major exogenous source of cyanide in Europe, he suggested cyanide as a possible precipitant of visual loss in LOA. This impression was reinforced by the observation that optic neuritis occurs as a result of cyanide intoxication from ingestion of bitter cassava in man[2,3] and in animals.[4] These findings prompted a search for abnormal cyanide metabolism in LOA.

Wilson[1] observed significantly increased urinary thiocyanate excretion in healthy smokers as compared with that in non-smokers. By contrast no difference between smokers and non-smokers was found in LOA patients, suggesting that patients with LOA are unable to respond to an increased intake of cyanide by increased detoxification. Rogers[5] also observed relatively low levels of thiocyanate in patients with LOA.

Significantly reduced rhodanese (Ec: 2.8.1.1) activity, the key enzyme for cyanide detoxification, was found by Cagnianut *et al.*[6] in the liver parenchymal cells and by Poole and Kind[7] in the rectal mucosa of patients with LOA. However, Wilson[1] reported normal rhodanese levels in the liver, Syme *et al.*[8] in the red cells, and Nikoskelainen *et al.*[9] in mitochondria of muscle samples of patients with Leber's disease.

These observations prompted this further study of cyanide metabolism in patients with LOA.

Case report

In mid-January 1985 a 22-year-old male non-smoker noticed decreased vision in the left eye followed by a decrease in the right eye two weeks later. The visual acuity was 20/200 in the right eye and 20/300 in the left eye. The right optic disc of the patient was hyperaemic, with blurred margins. Circumpapillary telangiectatic microangiopathy, tortuosity of the retinal vessels, and swelling of the retinal nerve fibres were apparent. No abnormal vascular permeability was demonstrable by fluorescein angiography. In the left eye the optic disc was blurred only nasally.

At that time general examination (including urine tests), neurological examination, CT scan, and the flash electroretinogram (ERG) were normal. The mother and the grandmother of the patient had also suffered acute visual loss in the 4th decade of life and both were more severely affected than the propositus. Cyanide levels were determined according to the method described by Pranitis and Stolman,[10] as modified by Wicht.[11] Rhodanese (a mitochondrial enzyme) activity was measured in white blood cells by Sorbo's method.[12]

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*Parts of the results were presented at the 83rd meeting of the German Ophthalmology Society and at the ARVO meeting 1987

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A significantly increased blood cyanide level of 1·4 µg/ml (54 µmol/l) was found in the patient at the first examination (normal level <0·2 µg/ml (7·7 µmol/l). In an attempt to lower the blood cyanide level the patient was treated for two days with 250 mg p-DMAP (which forms met-Hb), 600 mg CO_2-EDTA, 18 g vitamin B_{12} (which both complex cyanide), and 375 ml of 8% sodium thiosulphate infusion (substrate for rhodanese). With this treatment the blood cyanide fell to 0·6 µg/ml (23 µmol/l). Because of cardiac side effects CO_2-EDTA was withdrawn. Treatment was continued with sodium thiosulphate, and the cyanide level returned to normal after four weeks (Fig. 1). Treatment was then stopped and the blood cyanide level rose to 0·8 µg/ml (30·8 µmol/l). The visual acuity with each eye gradually deteriorated to 20/600 over the next three months. Treatment with sodium thiosulphate was begun again in July 1985, and cyanide levels returned to normal values. The level remained normal after cessation of treatment (Fig. 1). By September 1985 the visual acuity with each eye remained at 20/600, and the optic discs were pale.

An additional 12 patients with chronic LOA (including the mother of the patient reported on above) were tested White blood cell rhodanese activities and blood cyanide levels of all these patients were within the normal range.

Discussion

Our observation that the cyanide level was increased in a patient with acute LOA lends further support to the suggestion of Wilson[1,13] that there is a defect in cyanide metabolism. We could not induce any improvement in visual acuity despite adequate reduction of the blood cyanide levels. The late onset of the treatment (two weeks after the second eye deteriorated) may explain the absence of visual recovery. It is remarkable that an increased cyanide level was observed only in the acute stage. In each of our chronic cases cyanide levels were normal, and in our patient with the acute disease it returned to normal after the attack In contrast to the findings of Cagnianut *et al.*[4] and Poole and Kind,[7] none of our patients with LOA showed any reduction in rhodanese activity.

The finding in the patient with the acute disease implies a self-limiting derangement of cyanide metabolism. This would be in accordance with the behaviour of the disease in which acute dysfunction may or may not occur in patients with the abnormal inherited factor and funduscopic abnormalities.[14,15] These observations also imply that a metabolic abnormality may be detected only during the acute stage, and that normal activity of enzymes involved in cyanide metabolism outside the acute stage of the disease would not necessarily exclude abnormal enzyme activity as contributing towards the pathogenesis of the disease.

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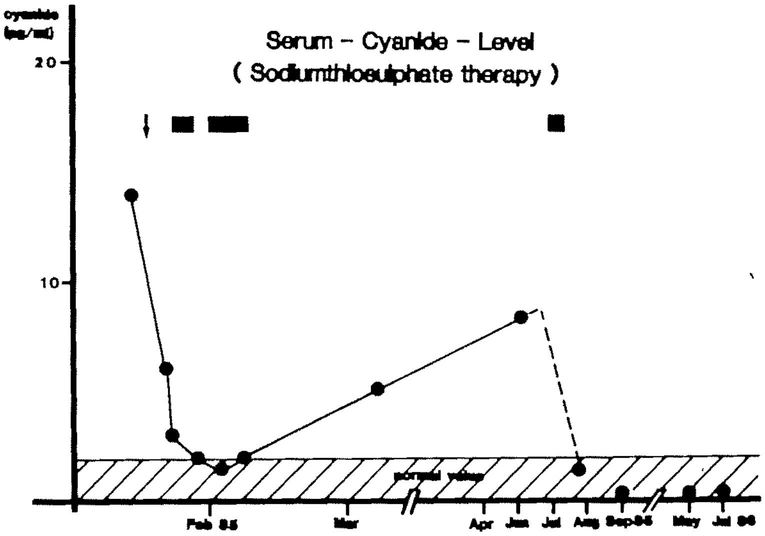

The change of the cyanide level during the therapy is shown The arrow indicates the initial therapy (600 mg CO_2-EDTA, 250 mg p-DMAP, 18 g vitamin B_{12}, 375 ml of 8% sodium thiosulphate infusion). The black blocks indicate the treatment with sodium thiosulphate infusion The first block presents a 4-day treatment, the second and third block an 8-day treatment, of 375 mg of 8% sodium thiosulphate infusion per day. The visual acuity was 20/300 in the right eye and 20/400 in the left eye at the beginning of the treatment In March 1985 the visual acuity had decreased in the right eye to 20/400 and in the left to 20/600 in parallel with the increase of the cyanide level. Just before the third treatment the visual acuity had decreased also in the right eye to 20/600.

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Ocular horn

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SUMMARY The case of a horn-like hyperplasia of the caruncle of the left eye in a 3-month-old child is reported. An atavistic origin of this growth as a vestigial upper incisor is suggested from the anatomical location of the horn.

Hyperplasia of the caruncle is a rare congenital abnormality rarely noted in the literature.[1,2] We report a case of hyperplasia of the caruncle in the form of a horn in a young child.

Case report

A 3-month-old male child was brought to the hospital owing to an abnormal growth from the left eye. The growth had been noted a few days after birth and had been gradually enlarging.

On general physical examination the child did not have any other congenital abnormality of the face or body. The right eye was normal on examination also. Examination of the left eye showed a horn-like growth 1·3 cm long arising from the caruncle (Fig. 1). The growth was conical, thicker at the base and tapering upwards. It was directed forwards and upwards. The upper two-thirds of the growth were dry and keratinised. The lower one-third was fleshy and moist. The medial canthus was somewhat displaced nasally. The upper and lower lids showed colobomas above and below the growth. Both upper and lower puncta were present. The eyeball was slightly displaced laterally. The rest of the ocular examination gave normal results. Testing the mobility of the growth under general anaesthesia showed it to be partially adherent to the eyeball. No abnormal conjunctival or episcleral blood vessels were seen feeding the growth.

The growth was shaved off from the episclera and examined histopathologically. It was found to consist largely of connective tissue, rich in elastic fibres, containing scanty adenoid tissue at one place only, and was covered with stratified columnar epithelium (Fig. 2). At one end of the section the epithelium was stratified cuboidal and keratinised. No germinal lymph follicles or muscle fibres were seen in the mass. No large blood vessels were seen.

Discussion

The clinical picture and histopathological examination pointed to a developmental overgrowth of the caruncle in the form of a horn. The caruncle develops independently at the end of the third month of gestation after the lids have fused. Classically it has been described as being formed by the cutting off of the inner part of the margin of the lower lid by the

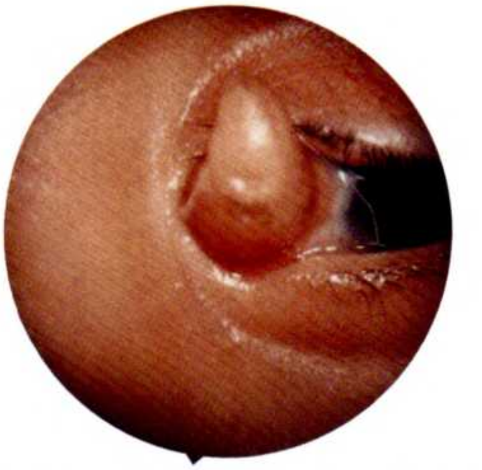

Fig. 1 *Horn-like growth arising from the caruncle of left eye.*

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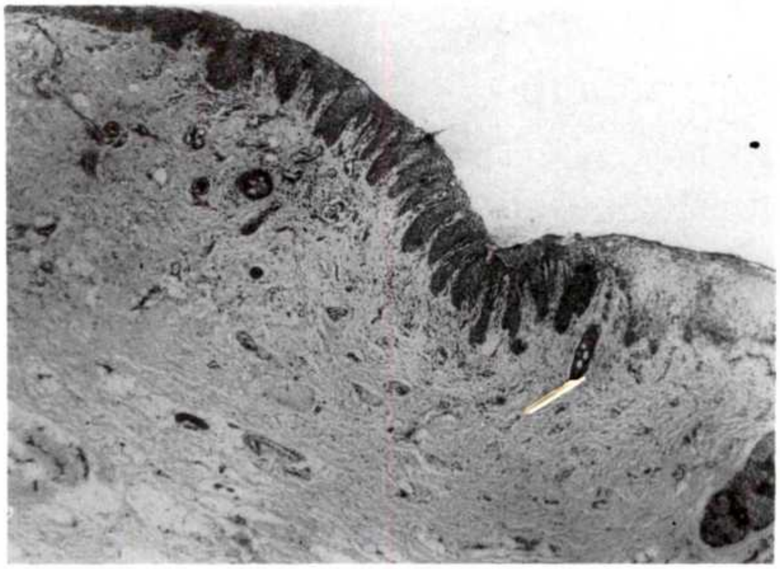

Fig. 2 *Histological section of the growth showing abundance of connective tissue covered by stratified columnar epithelium. On the right side of section the epithelium is cuboidal and keratinised. Haematoxylin and eosin, ×48.*

development of the inferior canaliculus and has been therefore said to be absent in animals with no lacrimal passages.[3] Papamiltiades,[4] however, found that it is developed at the end of the third month by cellular proliferation of the epithelium of the posterior surface of the medial part of the lower lid near its upper free border. Leplat *et al.*[5] agreed with such an independent origin. The presence of colobomas of the upper as well as lower lid in our case, with hyperplasia of the caruncle, does not support this view. It appears that in our case the cellular proliferation of the caruncle continued even after birth, giving rise to the abnormal growth.

The possibility of an atavistic origin of this horn-like growth cannot be ruled out. The anatomical location of the horn was similar to that of the tusks of elephants. Elephant tusks are greatly enlarged upper incisors (appendages of skin) which are situated on the medial side of the eyes and lateral to the trunk (a greatly enlarged and more sensitive nose). These tusks are surrounded by a pouch of skin. On this view one would have to consider the caruncle to be a vestigial remnant of the upper incisor of lower animals.

Acknowledgment is due to Dr Tagrit Mohamed for kindly referring this patient.

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Correspondence

Unfixed reference, monocular occlusion, and developmental dyslexia—a critique

Sɪʀ, I would like to respond to Dr D V M Bishop's criticisms[1] of my hypothesis that disordered vergence control causes poor visual direction sense, and is therefore a potent cause of children's reading problems.[2,3] I provided Dr Bishop with the full data on which our paper published in the *Lancet*[2] was based in order to try to convince her that monocular occlusion can help many dyslexic children to improve their fine vergence control, following which their reading often improves. So I am naturally disappointed with her conclusions.

Dr Bishop makes three main points, namely: (1) there is no evidence of a specific link between unstable vergence control and reading disability, once age and intelligence have been accounted for; (2) there is no evidence that dyslexics with unstable vergence control make visual localisation errors of the kind expected from our hypothesis, (3) there is no evidence that monocular occlusion in children with unstable vergence control helps them to improve their reading Hence she concludes that there is no evidence that poor vergence control is a cause of poor reading I will deal with each of these assertions separately

1 Is there a link between unstable vergence and poor reading?

Dr Bishop and colleagues were actually the first to publish in 1979[4] the results of a study of 147 unselected primary school children which showed clearly that children with unstable vergence control, as revealed by the Dunlop test, tended to be worse readers than those with good vergence control. However, she found that the children with poor binocular control tended to have lower intelligence than their peers, so she suggested that their lower intelligence was in fact the explanation for their poor reading, and that not understanding the test rather than poor binocular control explained their unstable Dunlop test responses However, Bishop *et al* assessed the children's intelligence using the full scale WISC, the verbal components of which are well known to penalise poor readers disproportionately. Hence the apparently lower intelligence of her subjects who gave unstable Dunlop test responses may well have been the result of their reading badly rather than the cause of it. Since that time several studies have been published, as Dr Bishop admits, which show conclusively that there is a strong association between unstable vergence control and poor reading[3,5] even when differences in chronological age, performance mental age, and reading experience have been accounted for Thus, contrary to Dr Bishop's conclusion, there is in fact good evidence of a strong link between poor binocular control and poor reading.

2 Evidence that children with unstable vergence make 'visual' errors

In our 1985 study[2] we found that dyslexic children with unstable vergence tended to make more visual than auditory errors when attempting to read, whereas dyslexics with stable vergence tended to make more auditory than visual errors. We found that many dyslexics made both types of error, however, probably because vergence instability was only one of their problems. Those who made equal numbers of visual and phonemic errors were the children who also tended to make sequencing errors. (We did perform a sequencing test, contrary to Dr Bishop's assertion.[1] She also states that we had found no difference in the requirement for speech therapy between children with unstable and stable vergence control, whereas we state clearly that 40% more of the latter (auditory dyslexics) had been given speech therapy.)

Dr Bishop criticised the lack of a non-verbal spatial discrimination test in our 1985 paper,[2] but she does not mention our recent studies (to which I have drawn her attention) in which we have shown conclusively that children with poor vergence control are very significantly worse at dot localisation tasks than IQ, chronological age, or reading age matched controls.[6] Thus, again contrary to Dr Bishop's conclusion, there is in fact good evidence that children with unstable vergence control make the kinds of visual localisation errors which one would expect from my hypothesis.

3. Evidence that monocular occlusion results in improved reading

It should be noted that neither Dr Bishop nor anyone else has disputed our finding that monocular occlusion helps about half of children with initially unstable vergence to gain good control within six months.[2] The question is whether this ocularmotor development is followed by improved reading. Here it seems to me that Dr Bishop reverses her previous arguments. In 1979 she thought that children with unstable vergence were of lower intelligence and that the latter, rather than poor binocular control, was what explained their poorer reading. However, she is now claiming that the reading progress of children with unstable vergence whose binocular control improved after monocular occlusion can be entirely explained by their having higher reading ability (ie, higher intelligence) to begin with.

To support this argument she has transformed our reading deficit measures to T scores. In our 1985 paper we chose to use (reading age minus chronological age) as our measure of reading deficit rather than reading T scores, because the latter have several drawbacks. First, calculation of a child's T score depends on the assumption that reading ability is normally distributed around the mean for a particular chronological age. But this is probably not true of the reading of dyslexic children.[7] Second, we felt that the T score is a very insensitive measure of reading ability. Children over the age of 9 are grouped in six-monthly bands which has the unfortunate effect of equating the scores of children of similar reading ability whose ages are six months apart. Moreover the T score range has a floor value of only −2 SDs from the mean, whereas the region of interest when considering dyslexics lies lower than this. Nevertheless, Dr Bishop transformed our measurement of reading deficit into T scores. So we do not find it surprising that using this blunt instrument she missed the real reading progress which some children make after developing stable vergence control

In our 1985 paper[2] we confirmed the clear relationship which many people have shown to exist between IQ, initial reading age, and reading progress. The effect of Dr Bishop's choosing to analyse reading T score changes has been to highlight this strong relationship and to bury the improvement which those who achieved good vergence control experienced. Using our more sensitive reading deficit score we were able to show by means of matched pairs and multiple regression analyses that the reading improvement of children whose vergence control became stable was highly significant, and independently of their initial reading age or their performance IQ. Thus, contrary to Dr Bishop's assertion, there is strong evidence that monocular occlusion not only improves the binocular control of many dyslexic children but also helps them to learn to read

In conclusion we have shown that Dr Bishop was probably mistaken in her 1979 conclusion that children with poor vergence control were of low intelligence and that this was the cause of both their unstable Dunlop test responses and their poor reading. The weight of more recent evidence shows that poor binocular control can lead to poor reading in children of both high and low intelligence, because such children are unable to localise small visual targets, such as letters, accurately. We have presented strong evidence that monocular occlusion can help many of these children to develop good vergence control, and that this is often followed by rapid reading improvement. We will shortly publish further results confirming that assisting children to develop good binocular control often helps them to learn to read.

But poor visuomotor control is not the only problem suffered by dyslexic children; many have phonemic segmentation difficulties in addition.[8] Hence identifying the visuomotor component of their reading problems will remain difficult, and arguments about its significance will continue. But I believe there is now little doubt that many children with reading problems do have binocular control abnormalities. These can be demonstrated objectively by means of eye movement recordings.[9] The onus continues to lie with us, of course, to prove that they are a cause of dyslexic children's problems, and that improving binocular control helps such subjects to improve their reading

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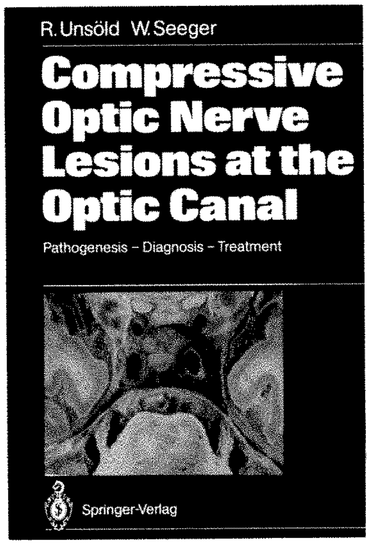

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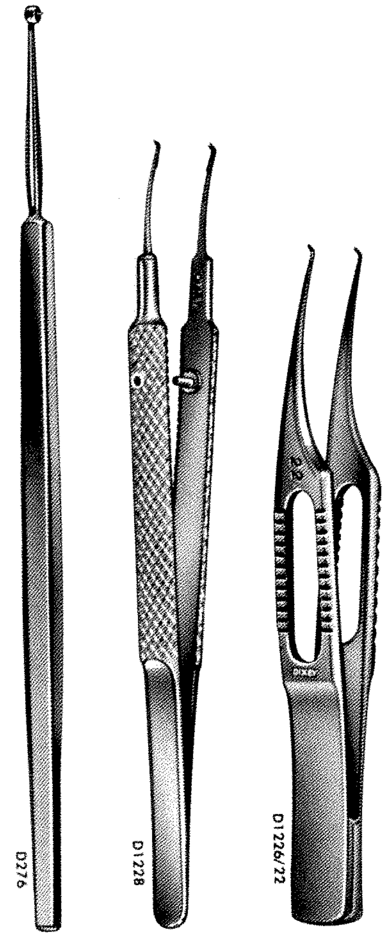

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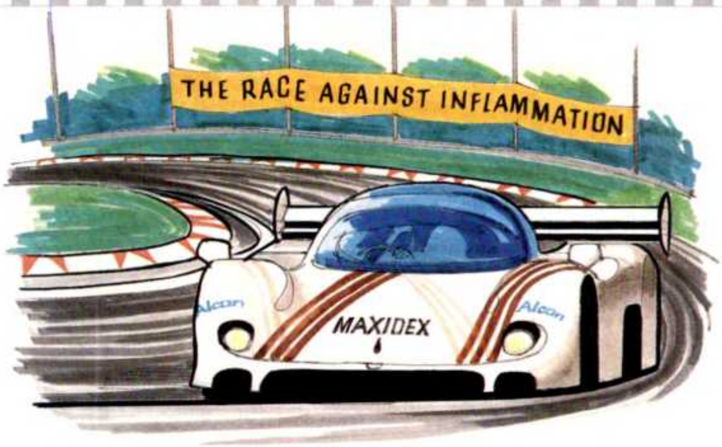

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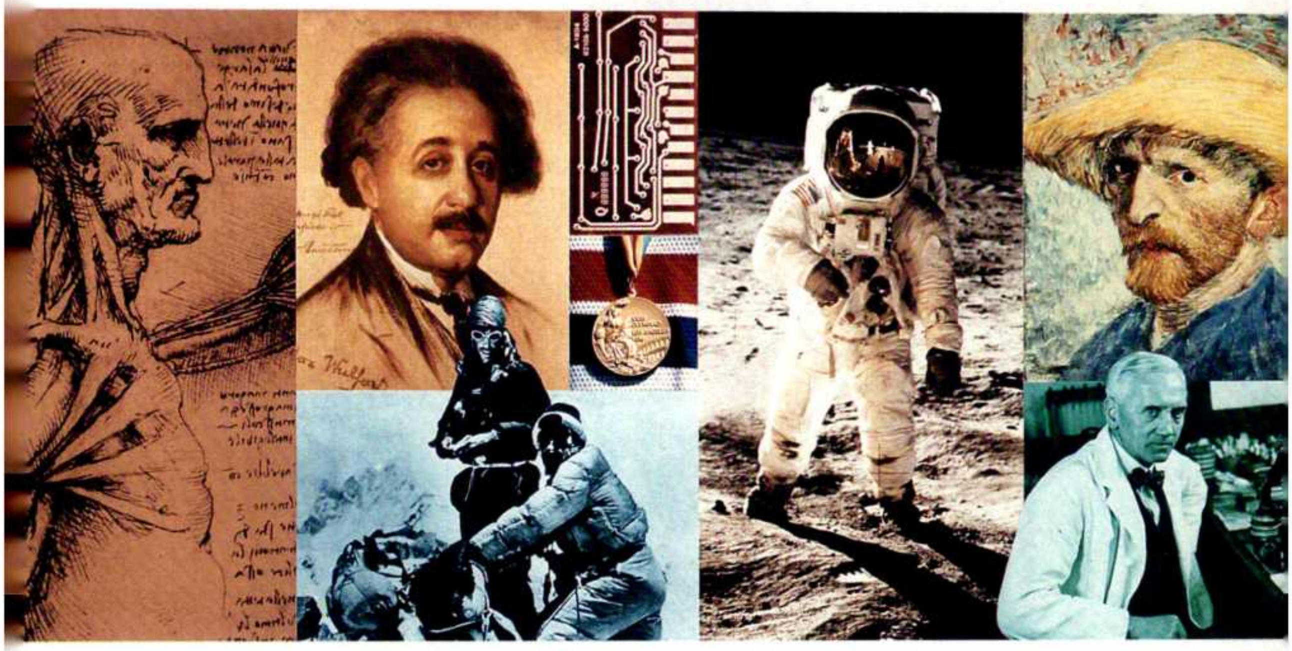

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British Journal of Ophthalmology, 1989, **73**, 321

Editorial: Waiting time for publication reduced

The *BJO* and similar scientific journals differ from most other types of publication in that they are written almost entirely by their own readers If readers want the quality of papers to improve, they must encourage their colleagues and themselves to submit high quality papers.

It might be thought from this preamble that I am about to complain of a shortage of papers, but this is not the case. My problem, paradoxically, has been an excess of papers which has led in its turn to a problem which has never occurred, at any rate in a serious form, to the *BJO* in its previous history. The waiting time for publication has got out of control.

I stand to be corrected but I do not believe my predecessors in this seat had any particular worries about an excess of papers or an unacceptable publication delay It was good enough to have the papers refereed in the usual way, accept papers of a sufficiently high standard, and let the publication time take care of itself. Indeed the journal has at certain times in the past even been short of papers.

Over the past three or four years this changed. Papers received by the journal increased in numbers dramatically, with the result that a publication delay, at its worst 13 months on average, built up. As soon as the trend became apparent urgent corrective action was taken in the form of much more stringent acceptance criteria, but it has to be realised that, once established, a long publication delay takes quite a long time to be shortened again.

I am happy to say that this has now been achieved, so that at the time of writing, namely the beginning of March, half the probable papers for the issue of October have been accepted and a new system for controlling the publication delay has been devised. The present delay of seven to eight months will be reduced rapidly to six months, and it is possible that an even faster turnround will be possible. In addition it is intended to run certain papers on a 'fast track' basis. Such papers will be limited to 2000 words and two figures and will be given priority. It will be up to authors to request fast track status, but the final decision whether it should be granted will be at the discretion of the editorial committee.

In controlling the acceptance-publication interval a 'diary' system rather than a waiting list will be used. This has been found to work extremely well in managing surgical waiting lists and I anticipate that it will be even better for this problem. Papers will be accepted provisionally for publication in a certain month ahead. Whether they are published then will depend on the authors' revising their papers to an acceptable standard in time for publication in the month provisionally allotted. Papers not ready in time will be deferred for publication at a later date. It must be emphasised that the monthly selection may exclude some meritorious papers. Thus the filling of the monthly quota will be on a competitive basis, although exceptionally a particularly meritorious paper for which there is simply not room may be deferred for a month Papers which we cannot fit in from the word go—not that there is necessarily anything wrong with them—will of course be rejected outright in the usual way.

To summarise, therefore: we have reduced the waiting time to seven to eight months and will soon have it down to six and will keep it strictly controlled. And a 'fast track' facility will be instituted.

RJHS

British Journal of Ophthalmology, 1989, 73, 322

Editorial: Graves' ophthalmopathy

'One of the most puzzling syndromes in ophthalmology is the variable and capricious exophthalmos which is associated with endocrine disorders. The cause and nature of the orbital changes . . . are still unknown.'[1] Duke-Elder, if he were with us today, might be excused for feeling that we had not made much progress since his comments of 1952, and even Graves[2] and Basedow[3] might not be particularly impressed. Our ignorance is certainly not for want of trying, as Duke-Elder tells us in the chapter referred to above that there had already been over 3000 papers on the subject by 1909.

Before the arrival of the concepts of immune responses (and autoimmunity in particular) much of the theorising concerned possible effects from various hormones, especially pituitary, but no one seemed to have much idea how they could produce such peculiar effects, apparently specific to the extraocular muscles. I well remember an embarrassing interview with an examiner during one of my attempts to obtain the fellowship of the Royal College of Surgeons of England, when it was apparent that he was just as confused on the subject as I was.

Teaching it to medical students was always a challenge. How do you explain that something which is associated with Graves' disease is even more likely to occur after thyroidectomy or even in hypothyroidism, where there has been no prior evidence of Graves' disease? I used to try and get around the teaching problem by telling students a bit of a fairy tale. I taught that some unknown substance, in the old days probably a hormone, leaked out from the pituitary and entered the orbit by some form of local diffusion. Once in the orbit it caused inflammation of the muscles, irritating the levator at first, hence the lid retraction, but eventually causing swelling and therefore exophthalmos, and finally sinking to the bottom of the orbit, where it caused fibrosis of the inferior rectus muscle. Although this story probably sounds naive to afficionados of the subject, of whom there appear to be a considerable number, nevertheless it is quite useful as a means of helping students to remember the sequence of events.

The paper by Weetman, Fells and Shine in this issue is an altogether more serious contribution to our understanding of the problem. In pursuance of the theory that the mechanism of Graves' ophthalmopathy is an autoimmune myositis with a specific expression in extraocular muscles, they have sought human eye muscle membrane binding antibodies in patients. However, as usually seems to be the case in this tantalising condition, the results only give rise to more questions. For example, why are the antibodies found in patients with thyroid autoimmunity regardless of eye signs, and how is it that the antibodies bind equally well to skeletal muscle? In other words, they are not site specific. Perhaps the fairy story I used to tell the students had some truth in it after all.

REDMOND J H SMITH

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British Journal of Ophthalmology, 1989, **73**, 323–327

T and B cell reactivity to extraocular and skeletal muscle in Graves' ophthalmopathy

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SUMMARY We have sought human eye muscle membrane binding antibodies in patients with Graves' ophthalmopathy using an enzyme-linked immunoassay. Antibodies were found in patients with thyroid autoimmunity irrespective of eye signs, and binding correlated closely ($r=0\cdot94$) with binding to skeletal muscle, showing that these antibodies are not site-specific. T cells from patients with thyroid autoimmunity proliferated in response to eye muscle, but again this was not specific for eye muscle or the presence of ophthalmopathy. No single antigen was responsible for inducing proliferation. These results fail to confirm a recent report of eye muscle membrane binding antibodies in a high proportion of patients with ophthalmopathy, and suggest instead that T and B cell autoreactivity to striated muscle antigens is a frequent feature of autoimmune thyroid disease, unlikely to be directly related to eye disease.

Graves' ophthalmopathy appears to be an autoimmune disease, but despite extensive studies, reviewed recently,[1] the immunological mechanisms responsible for the condition have not yet been elucidated. Studies of both retrobulbar pathology and the evolution of disease as revealed by CT scanning have shown that the extraocular muscles are the primary site of involvement.[2] The eye muscles become infiltrated by lymphocytes early in the course of disease, with subsequent oedema; this leads to fibrosis and muscle fibre atrophy later.

Further understanding of Graves' ophthalmopathy should come from elucidation of the antigens recognised by these autoreactive cells, since this would aid identification of the pathogenic components of disease – for example, whether autoantibodies or cytotoxic cells are involved. The possibility that antibodies against eye muscle antigens are a feature of ophthalmopathy was suggested by recent studies using porcine eye muscle as an antigen in an enzyme linked immunosorbent assay (ELISA) in which 64% of patients with Graves' ophthalmopathy were positive, compared with only one of 22 Graves' disease patients with no clinical evidence of eye disease.[3] However, others have failed to obtain such clear results,[4,5] and the possibility exists that species differences may preclude reactivity of positive human sera in such an assay. T cell responses to retrobulbar antigens have also been assessed by a variety of assays, but again with conflicting results.[6-8] The T cell proliferative response to retrobulbar antigens has not to our knowledge been assessed previously, though this is a simple test of T cell sensitisation; lacrimal gland extracts do stimulate T cell division in about 40% of Graves' ophthalmopathy patients.[9]

In the present study we have tested T and B cell reactivity to human skeletal and eye muscle antigens, using proliferative responses and an ELISA respectively, with the aims of identifying any autoantigens which are unique to the eye and which elicit responses only in patients with Graves' ophthalmopathy.

Materials and methods

PATIENTS

Samples were obtained from the following group of subjects (1) Graves' ophthalmopathy (n=23, three men), mean age (SD) 58(15) (range 14–84), all with grade III or greater eye changes,[10] which were active or had been treated within the preceding six months Nineteen patients also had Graves' disease; the

Correspondence to Dr A P Weetman

remaining four were ophthalmic Graves' disease, with hypothyroidism in three. (2) Graves' disease (n=18, seven men), mean age 40(14) (range 19–65), all with minimal (grade 0-II) eye changes; 11 were untreated and seven were receiving carbimazole, (3) Hashimoto's thyroiditis (n=14, two men), mean age 50(17) (range 19-75). (4) Normal controls (n=16, six men), mean age 36(12) (range 18-52) taken from hospital staff with no history of thyroid disease.

ANTIGEN PREPARATION

Snap-frozen extraocular muscle (EM) from surgery for an intraocular malignancy, and skeletal (arm) muscle (SM) from an amputation, were minced and homogenised at 4°C in phosphate-buffered saline (PBS), pH 7·4, in a Polytron homogeniser (Kinematika, Lucerne, Switzerland). The homogenates were spun at 2000 g for 20 minutes at 4°C and the pellets discarded. The supernatants were further centrifuged at 10 000 g for 40 minutes at 4°C and the resulting membrane fractions, in the pellets, used as antigens. The protein concentration in each antigen was determined spectrophotometrically with Coomassie blue G250[11] and the antigens stored in aliquots at −70°C.

ELISA

Preliminary experiments revealed that both antigens contained IgG in concentrations sufficient to cause high background readings in the ELISA. Prior to coating assay plates, therefore, the antigen preparations were sonicated (4×15 s at 15 kHz) on ice and then incubated with Protein-A-Sepharose beads from Pharmacia, Uppsala, Sweden (1 mg antigen in 1 ml PBS with 0·5 ml packed beads) for 15 minutes on a rotator; antigen was recovered by centrifugation and used to coat ELISA plates overnight at 4°C with 10 μg antigen/ml coating buffer (carbonate buffer; pH 9·6). The next morning the plates were washed and blocked with 3% bovine serum albumin (BSA) in PBS for 1 hour. Serum was tested at 1:100 dilution in PBS-0·05% Tween 20 After two hours at room temperature the plates were washed and incubated with 1:1000 dilution of antihuman IgG alkaline phosphatase conjugate (Sigma) for a further two hours After the washing a substrate (*p*-nitrophenyl phosphate 1 mg/ml in carbonate buffer plus $MgCl_2$. 100 μg/ml, pH 9·6 was added and the absorbance at 405 nm read on a Titertek Multiskanner (Flow Labs, Irvine, Scotland). Results are the mean of duplicate estimates. Variation between duplicates never exceeded 15% and was usually less than 10%.

BLASTOGENESIS

Peripheral blood mononuclear cells (PBM) were isolated on Ficoll-Hypaque gradients and incubated at 10^5 cells/well of a 96-well flat-bottomed plate in 200 μl final volume of culture medium (RPMI 1640 with 10% fetal calf serum). Sonicated muscle antigens (sterilised by irradiation) were added in varying concentrations at the beginning of culture. After four days [^{3}H]-thymidine, 1 μCi/well, was added and the cells harvested on to filters 16 hours later; [^{3}H]-thymidine incorporation was measured by liquid scintillation counting and results expressed as counts per minute (cpm) All assays were performed in triplicate, and control as well as patient lymphocytes were included in each set of cultures.

To delineate putative antigens further we used the fractionation method described by Abou-Zeid *et al* [12] In brief, muscle antigens were separated on a 5-15% sodium dodecyl sulphate (SDS)-polyacrylamide gradient gel and transferred electrophoretically to nitrocellulose; conditions were as defined previously for porcine eye muscle.[5] The transferred proteins were then divided into 4 mm band fractions by cutting the nitrocellulose into 20 pieces, 4 mm deep and 10 mm wide. These pieces were dissolved in dimethylsulphoxide and resuspended, in particulate form, in 1 ml carbonate buffer, pH 9·6. The fractions were then washed, resuspended in culture medium, and used at 20 μl/well for stimulation of blastogenesis.

Results

ELISA

The results of antibody binding to EM by ELISA are shown in Fig 1. With the mean absorbance of the control sera plus 2 SD taken as the upper limit of normal, 2(11%) of the ophthalmopathy sera gave

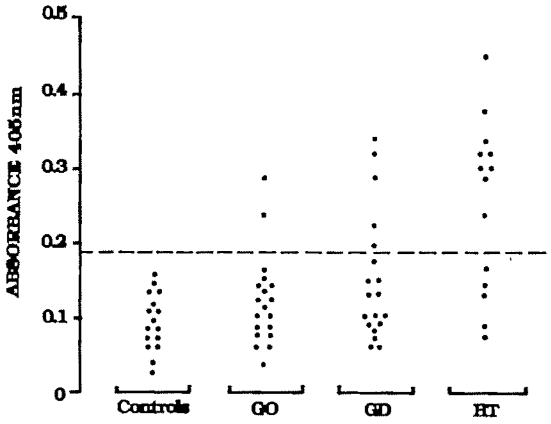

Fig. 1 *ELISA using eye muscle as coating antigen. The dotted line represents 2SD above the control mean. GO=Graves' ophthalmopathy, GD=Graves' disease, HT=Hashimoto's thyroiditis*

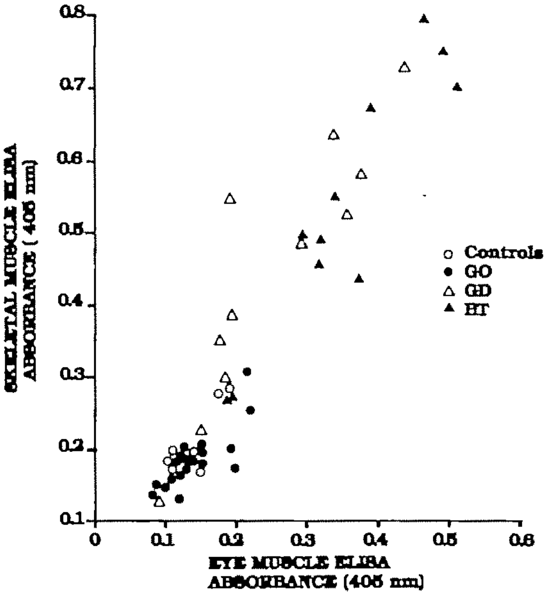

Fig. 2 *Correlation between ELISA for reactivity against eye and skeletal muscle; r=0·94, p<0·0001 GO=Graves' ophthalmopathy, GD=Graves' disease, HT=Hashimoto's thyroiditis*

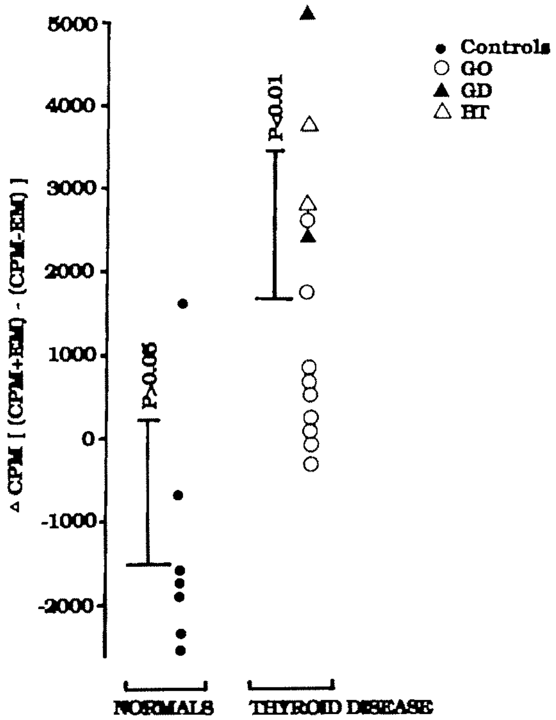

Fig. 3 *Blastogenic response of peripheral blood T cells to eye muscle membranes (100 µg/ml) Results are shown as the difference in cpm between cultures with and without antigen To the left of each column is the group mean +1 SD. Probability values are given for a paired t test between cultures with and without antigen. GO=Graves' ophthalmopathy, GD=Graves' disease, HT=Hashimoto's thyroiditis.*

positive binding, compared with 4(22%) of the Graves' disease sera and 9(64%) of the Hashimoto's disease sera. The absorbance values did not differ significantly between controls and Graves' disease patients with or without ophthalmopathy, but the Hashimoto sera absorbances were significantly higher than those of controls (p<0·01, Wilcoxon rank test). When the absorbances produced by binding to EM were compared with those agianst SM, a signficant correlation was found, as shown in Fig 2 (r=0·94, p<0·001).

T CELL BLASTOGENESIS

Using 100 µg of EM/ml culture medium, we found the PBM from thyroid disease patients (n=13) showed significant stimulation of proliferation over background (p<0·01, paired *t* test), but this had no obvious relationship to the presence of eye signs. These results are shown in Fig. 3 as the difference in cpm between cultures in the presence and in the absence of antigen. By comparison, PBM from control subjects (n=7) showed no stimulation with EM antigen. The response was dose dependent, being maximal at 100 µg antigen/ml (Table 1). Again there was a significant correlation between the blastogenic response to EM and SM, both at 100 µg/ml, as shown in Fig. 4 (r=0·98, p<0·001).

To identify further the antigens responsible for stimulating T cell proliferation the EM was fractionated by polyacrylamide gel electrophoresis; 28 bands were identifiable by Coomassie blue staining. These were all transferred to nitrocellulose as verified by amido black staining of the nitro-

Table 1 *Dose response for various concentrations of eye muscle antigen in T cell blastogenesis*

		Antigen concentration (µg/ml)			
	Patient	*Nil*	*100*	*10*	*1*
Graves' ophthalmopathy	1	538*	932	701	517
	2	1105	1863	1487	1298
	3	193	2866	352	NT
	4	939	1202	1572	1302
Graves' disease	1	5549	10800	5588	NT
	2	4213	6767	4165	NT
Hashimoto's thyroiditis	1	1089	5013	3164	NT
	2	1695	4537	2314	NT

*Values are mean (of triplicate) cpm. Replicates were always within 15% of the mean. NT=not tested

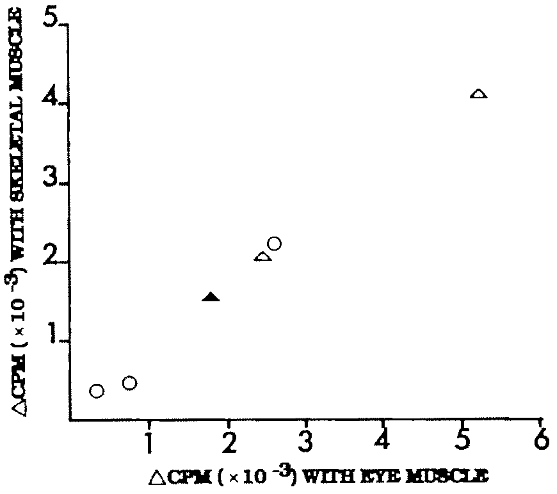

Fig. 4 *Correlation between the blastogenic responses to eye and skeletal muscle both at 100 μg/ml, $r=0\cdot98$, $p<0\cdot001$ Results are expressed as in Fig. 3. The open circles are patients with Graves' ophthalmopathy, the open triangle Graves' disease, and the solid triangles Hashimoto's thyroiditis.*

cellulose. The dissolved fractions corresponding to the separated antigens were added to cultures of PBM from seven patients with ophthalmopathy and two patients with Hashimoto's thyroiditis; control cultures were also set up with nitrocellulose free of antigen. In five sets of cultures there was no striking stimulation of T cell proliferation with any single fraction, though in all cases some fractions stimulated proliferation 2-3 fold above the control values. In the remaining four cultures stimulation was seen with certain fractions that was 4-13 fold above control values (Table 2). These fractions were numbers 2 and 3 (approximate MW 72-78 kd) for 2 patients, 5 and 6 (approximate MW 52-56 kd) for one patient, and fraction 20 (approximate MW 12 kd) for the other patient. This latter patient had Hashimoto's thyroiditis. It can be seen in Table 2 that there was often considerable variability between the triplicates, reflected by a high SD; this probably represents a low precursor frequency of cells responsive to certain antigens, as discussed by others.[12]

Table 2 *Blastogenic responses to fractions of eye muscle*

Patient	*Nil*	*Plus antigen (fraction number)**
1	2319 (465)†	23175 ± 15883 (2)
		27688 ± 2721 (3)
2	1089 (402)	10743 ± 1742 (2)
		9193 ± 2488 (3)
3	842 (464)	8645 ± 2665 (5)
		11281 ± 708 (6)
4	2343 (565)	10253 ± 9231 (20)

*Numbers in parentheses are the fraction number used to stimulate blastogenesis; other fractions gave stimulation of less than four times control values

†Results are mean cpm(SD)

Discussion

These results show that B and T cells are sensitised to eye muscle antigens in patients with autoimmune thyroid disease, irrespective of clinically apparent ophthalmopathy, and these antigens are common to striated skeletal muscle. We have used a human eye muscle antigen preparation, in contrast to previous studies with porcine material[1-5]; this gave a low background once IgG had been removed. Previous studies with human eye muscle membranes have given conflicting results in an assay using protein A to detect immunoglobulin binding, but IgG was not depleted prior to using the antigen.[13 14] Our results confirm recent studies showing that porcine muscle membrane-binding antibodies are not tissue specific.[4 5] In the present series only the group of patients with Hashimoto's thyroiditis showed significantly higher binding than controls. Patients with thyroid autoimmunity also have antibodies against tubulin[15]; possibly this and other cytoskeletal antigens are being detected in the ELISA. The greater reactivity of the Hashimoto's group could reflect heightened and broader autoreactivity in these patients.

We also examined T cell sensitisation to muscle antigens by measuring proliferation. Patients with thyroid autoimmunity, again irrespective of eyes signs, gave a positive response, and this also was not specific for extraocular muscle. With the migration inhibition factor assay and a retrobulbar connective tissue antigen, 30-60% of Graves' disease patients without ophthalmopathy gave a positive response, in addition to the positive responses in 90-100% of ophthalmopathy subjects.[8 16] To our knowledge T cell proliferation with extraocular muscle has not been assessed previously, though 41% of ophthalmopathy patients did give a blastogenic response to a lacrimal gland extract.[9] The present findings show in addition that T cells may be sensitised to several different antigens within these crude membrane preparations, as revealed by the fractionation studies. No single molecular weight determinant was found which reliably produced proliferation, but fractionated antigens with molecular weights of about 75, 55, and 12 kd warrant further study.

In summary, our results do not confirm the existence of ophthalmopathic immunoglobulins in Graves' ophthalmopathy,[1] but they show instead that thyroid autoimmunity is associated with B and T cell reactivity to striated muscle antigens of either extraocular or skeletal muscle origin. This makes the strong association of Graves' disease, but not Hashimoto's thyroiditis, with ophthalmopathy difficult to understand, unless the unknown sensitising antigen (which could be thyroid or retrobulbar in origin) induces a response only in Graves' disease patients:

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Frozen section control of excision of eyelid basal cell carcinomas: 8½ years' experience

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SUMMARY For a period of 8½ years all basal cell carcinomas were excised under frozen section control. One hundred and fifty-six patients with 165 tumours were treated, and 137 were followed up for at least three months (3–94 months, mean 29·1 months). There were three possible recurrences, giving a recurrence rate of up to 2·19%. The practical implications, advantages, and difficulties encountered are described, and the place of frozen section control of excision of basal cell carcinoma in a busy NHS general ophthalmic practice is discussed.

Recurrence of basal cell carcinoma after surgical excision is generally believed to be due to inadequate excision of the tumour. This has been shown to occur in an unexpectedly high percentage of cases—23% reported by Aurora and Blodi[1] and 50% by Rakofsky.[2] Mercifully, recurrence occurs in only one-third or less of inadequately excised cases, for example, 23·4% in Rakofsky's series,[2] for reasons which are not well understood.

Surgery under histological control, ensuring complete excision of tumour, should theoretically eliminate the risk of recurrence in basal cell carcinoma. Older *et al*[3] reported a 100% cure rate from a series of 157 basal cell carcinomas, 72% of which had frozen section control, and complete resection was achieved in 97·5% of cases overall. Chalfin and Putterman[4] reported no recurrences from 37 primary and 16 recurrent basal cell carcinomas during follow-up of 3–48 months (mean 14·3 months), and 3–52 months (mean 22·6 months) respectively.

Doxanas *et al*[5] reported a study of 165 basal cell carcinomas. In 39 cases excised under frozen section control there were no recurrences, while among the remaining 126 cases excised without frozen section control 34 (26·9%) were incompletely excised and 7 (5·5%) recurred.

I decided to use frozen section control for all cases of basal cell carcinoma excised under my care until there were enough cases and sufficiently long follow-up to allow me to decide if the advantages of the technique justified the extra time and cost involved. The purpose of this paper is to report my experience in the hope that others will profit thereby

Material and methods

Excision of the tumour was witnessed by the pathology technician, marker sutures being used to facilitate orientation of the specimen in the laboratory. Frozen sections of the specimen were examined by the pathologist, who communicated his findings to the surgeon by telephone Paraffin sections were prepared and reported on later. If excision was incomplete, further tissue was excised from the appropriate margin. This was examined by frozen section in the early years of the project, but, as tumour was not found in most of the secondary specimens, latterly the tissue was placed in formalin for paraffin section examination, unless there was serious concern that the second excision might still be inadequate.

The frozen sections were prepared as described by Doxanas *et al*.[5] The specimen was bisected through the centre of the tumour and sections were taken in a plane parallel to that cut. Subsidiary planes were examined in large lesions or where the initial sections were inconclusive. The plane in which tissue was examined was varied in some cases at the request of the surgeon to include any particularly difficult margin. The method of Chalfin and Putterman[4] and Older,[6] in which marginal blocks are cut from every raw surface of the specimen and then sectioned, was not available.

Surgical reconstruction was delayed until the frozen section report was received, or started in such

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a way that further excision and more major repair could be done if necessary.

The patients were followed up for at least five years, longer if they were willing to continue to attend annually.

PATIENTS

The study was done in the context of a busy NHS general ophthalmic practice. All patients under my care undergoing surgery for basal cell carcinoma from April 1979 to 18 December 1987 were entered in the study.

During the period of the study 156 patients, all Caucasian, with 165 basal cell carcinomas were treated. Of these tumours eight were recurrent, the patient having been previously treated with radiotherapy, cryotherapy, curettage, or surgery. Seven patients had a past history of basal cell carcinoma, and 14 had more than one focus of tumour during the period of the study. Concurrent basal cell carcinomas not on the lids or adjacent face were treated by traditional methods, usually surgery without frozen section control.

Four additional patients were excluded. In two cases the frozen section showed doubtful clearance, but further excision was not done for the following reasons. One patient was too nervous and agitated under local anaesthetic (paraffin sections later confirmed complete excision). The other patient was aged 85 and had an upper lid basal cell carcinoma. Excision was macroscopically complete, and the pathologist was unsure of clearance because the tumour came very close to one margin of the sections. Further excision would have required a major plastic surgical repair and was not done because of the doubt and the patient's advanced age. Paraffin sections later showed that the original excision was just complete. The other two cases of incomplete excision were excluded because, although further tissue was removed, it was not sent for histology by the junior medical staff concerned, and the conditions of the study were not fulfilled. In none of the four cases has tumour recurred (follow-up 1–19 months, mean 10·8 months).

The patients were aged between 33 and 90 years old at the time of operation (Table 1). (Age at first operation is entered for those who developed further tumours at other sites.) The peak incidence was during the sixth and seventh decades, 31·4% and 33·3% respectively.

Table 1 *Age of patients*

Age (yr)	*Patients*	*%*
30–39	3	1·9
40–49	8	5·1
50–59	25	16·0
60–69	49	31·4
70–79	52	33·3
80–89	18	11·5
90–99	1	0·6

Table 2 *Site of tumour*

Site	*Number*	*%*
Lower lid	79	47·9
Medial canthus	45	27·2
Preseptal lower lid and cheek	15	9·1
Upper lid	13	7·9
Lateral canthus	8	4·8
Brow	4	2·4
Forehead	1	0·6

The tumours were located as shown in Table 2. The forehead tumour was included because it was excised under frozen section control at the same time as an eyelid lesion.

SURGICAL REPAIR

Unfortunately the dimensions of the tumours were not always recorded. However, the nature of the necessary surgical repairs (Table 3) is an indicator of the size of the lesions. Defects closed by simple releasing incisions, small local flaps, or lateral cantholysis are included in the primary closure group, which accounts for 65 lesions (40·1%). Ninety-one more major repairs were done (56·2%); three of these operations repaired the defect left after excision of two foci of tumour. Surgical details are not available in six cases (3·7%).

Results

Of the 165 tumours 137 have a documented follow-up of 3–94 months (mean 29·1 months). The remaining patients have died of other conditions, moved away, or failed to keep their appointments.

Three patients developed a new focus of basal cell carcinoma close enough to the site of the original tumour to be a possible recurrence. However, there

Table 3 *Method of surgical repair*

Method	*Number*	*%*
Primary closure	65	40·1
Full thickness skin graft	35	21·6
Temporal advancement flap	21	13·0
Upper lid pedicle flap	14	8·6
Mustardé cheek rotation flap	9	5·6
Cheek pedicle flap	7	4·3
Forehead or glabellar flap	3	1·9
Island skin graft	2	1·2
Details not available	6	3·7

For remaining three operations see text

are features in each case suggesting that these may be new tumours. These cases will therefore be described in detail.

CASE 1

A 60-year-old woman presented to me in November 1982 with a basal cell carcinoma below the lid margin at the lateral end of the right lower lid She said that basal cell carcinomas had been removed from this area 10 and three years previously. She had lived abroad in Egypt and West Africa for many years. The tumour was excised and repaired with an island skin graft brought in from the temple lateral to the eye. In January 1988 she had a nodular recurrence in the scar at the site of the original lesion. I regarded this as a straightforward recurrence until I reviewed her case and saw her dermatology notes from another hospital. In November 1983 I had found three more foci of basal cell carcinoma on the right side of the face, but as these were clear of the eye and site of surgery I referred her to the dermatologist. His notes show that three basal cell carcinomas were treated by curettage and cautery in January 1984—on the right eyebrow, right breast, and left thigh; in addition a large lesion was excised from the left thigh which was reported as being multicentric basal cell carcinoma The dermatology records show that 11 more foci on the face, neck, and limbs were treated by cryotherapy during 1985–7. One lesion on the shin had arisen in the scar of a previous injury. In view of this and the multiplicity of lesions there is reason to question whether the eyelid recurrence is a straightforward recurrence or perhaps a new focus.

CASE 2

A 57-year-old woman was referred from another regional centre with an extensive basal cell carcinoma of the right lower lid. Clinically the lesion was spreading along the lid margin, except for a central ulcer which extended 5 mm onto the pretarsal skin. Biopsy specimens had been examined twice prior to her referral. The first biopsy two years before had been reported as chalazion, the second, one month before, as basal cell carcinoma. Excision of seven-eighths of the lid with a Mustardé cheek rotation flap repair was performed in January 1985 Tumour was found extending to the temporal margin of the first specimen, but a further section of lid contained no tumour. All was well for one year, and then a granulating spot appeared in the vertical paranasal scar of the cheek rotation flap approximately 9 mm below the lid margin at the approximate level of the lower corners of the original rectangular resection, which were well away from the original tumour. (The skin along the base of the rectangle was excised to allow the cheek rotation flap to be swung in.) The spot failed to heal, so biopsy was done and showed basal cell carcinoma. Formal excision was carried out in April 1987 with full-thickness skin graft repair. Histology showed basal cell carcinoma with some squamous differentiation, and it was the pathologist's opinion that this was a new primary tumour.

CASE 3

A 71-year-old woman had a basal cell carcinoma occupying the medial third of the right lower lid including the punctum. The tumour was excised in the usual way, with the lower canaliculus being sacrificed, and a cheek rotation flap repair made. Another basal cell carcinoma appeared in the advanced lid 47 months later, near to but clear of the resection scar. After diagnostic biopsy the patient was referred for radiotherapy because her general health had deteriorated, and surgery would have involved a further major plastic repair.

The overall recurrence rate for the study would therefore be 2·19%, 1·46%, 0·72%, or 0% depending on how many of the three cases are counted as true recurrences.

HISTOLOGY

The usual time interval between excision of the tumour and telephoned histology report was approximately 25 minutes. This was in spite of the pathology laboratory being 4 miles (6 km) away. Sometimes, however, the delay was longer—up to 45 minutes on one occasion—if the specimen was large or awkward to section, so that many sections had to be cut and examined before the pathologist was able to report. All the sections were reported by experienced consultant pathologists.

Twenty-one specimens were reported as inadequately excised and further tissue was taken. Only three of the secondary specimens contained tumour, suggesting that in the other 18 cases the line of excision had passed just outside the tumour.

In one of the three cases showing tumour in the second specimen subsequent paraffin sections revealed that there were two tumours present. The first specimen contained all the clinically visible tumour and included part of a separate, macroscopically invisible tumour, the remainder of which was in the second specimen.

Another case, reported as completely excised on frozen section, was found to have a small, completely excised basal cell carcinoma with heavy lymphocytic reaction at the edge of the specimen on paraffin sections. This had been thought to be folliculitis or a cellular naevus on the frozen sections. There has been no recurrence (follow-up 10 months).

Table 4 *The author's incomplete excision rate for each year of the study*

	Total cases	*Incomplete excisions*	*% Incomplete excisions*
1979	7	2	28·6
1980	14	5	35·7
1981	14	1	7·1
1982	24	3	12·5
1983	13	2	15·4
1984	8	1	12·5
1985	20	2	10·0
1986	18	5	27·8
1987	26	4	15·4

EFFECT ON SURGEON

My ability to judge the extent of the tumour, as measured by complete excision on frozen section, improved as the study progressed (Table 4, in which my two incomplete excisions on frozen section described under 'Patients' are included). The immediate report and ability to localise the incompletely excised margin was invaluable in learning to assess the extent of lesions, but after 8 years and 144 cases my incomplete excision rate is still significant (Table 4).

The first recurrence was not until April 1986, when the study had been running for seven years. By this time my faith in frozen section control to confirm complete excision and eliminate recurrence had become very real, and there was a great temptation to skimp the 3 mm margin of macroscopic clearance when excising the lesions. This may account for my relatively high incomplete excision rate for 1986.

Discussion

This study was undertaken because I was impressed with the 100% cure rates for basal cell carcinoma reported when the tumours are excised under frozen section control.[3-5] A frozen section service was available, so I determined to run this study to evaluate the cost effectiveness and place of the method in an NHS general ophthalmic practice.

Sadly, it was not possible to achieve a 100% cure rate; the recurrence rate was up to 2·2%. A definite recurrence rate is not quoted because of uncertainty in three cases (one of which was a recurrent tumour) whether there was recurrence or new tumour. Recurrence rates of 2·3%,[7] 1·4%,[8] and 0·5%[9] have been reported in past series of primary tumours excised without frozen section control, but most series report higher rates. Rates for series of recurrent tumours are greater; Payne *et al*[10] reported 10% for primary tumours and 16% for recurrent tumours.

The way in which the histology is done is important. The method described by Chalfin and Putterman[4] is not generally available but is considered more accurate by some.[6,11] The presence in two cases of clinically invisible additional tumour in the edge of the excised specimen emphasises the multifocal nature of basal cell carcinoma. Even if resection lines can be guaranteed tumour free, adjacent foci may grow and simulate recurrence.

Collin[7] questioned the value of frozen section control for primary basal cell carcinomas because the generally reported recurrence rates for excision of these lesions are low. He also reported five cases which developed recurrent tumour even though histological examination showed complete clearance.

This study was conducted in the midst of a busy general ophthalmic practice. Frozen section control meant longer operating time for each basal cell carcinoma patient, longer lists for the surgeon and theatre staff, and slower clearance of other cases from the waiting list. This last disadvantage was minimised when our twin theatre suite came into operation and two patients could be dealt with simultaneously. Other less major basal cell carcinoma cases were done in the minor operations theatre at a different time. The pathology technician had to travel to the Eye Unit to collect the specimens, and the frozen section meant extra work for the laboratory.

CONCLUSION

In the light of this 8½ years' experience it is now my opinion that frozen section control is valuable and cost effective for tumours requiring a major plastic surgical repair, and for those with a worse prognosis such as recurrent tumours[7] and morphoea type lesions, the extent of which are extremely difficult to judge clinically, and which are aggressive if they recur.[5] I do not consider frozen section control cost effective or essential for every case.

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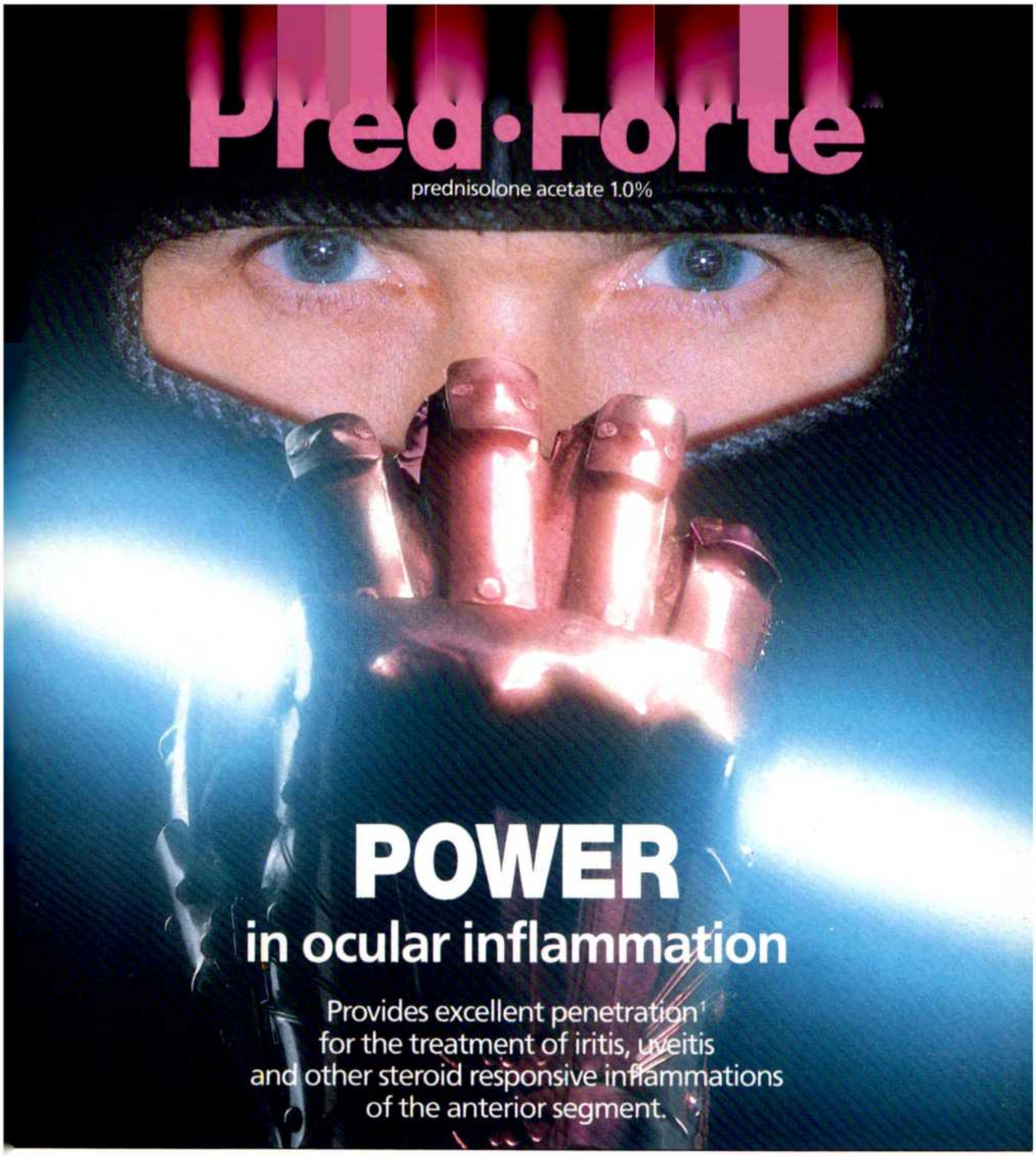
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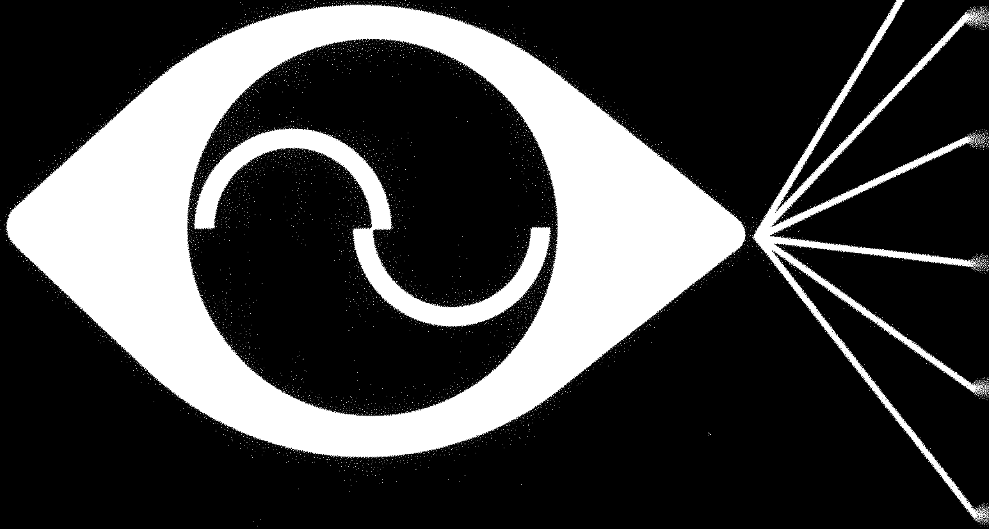

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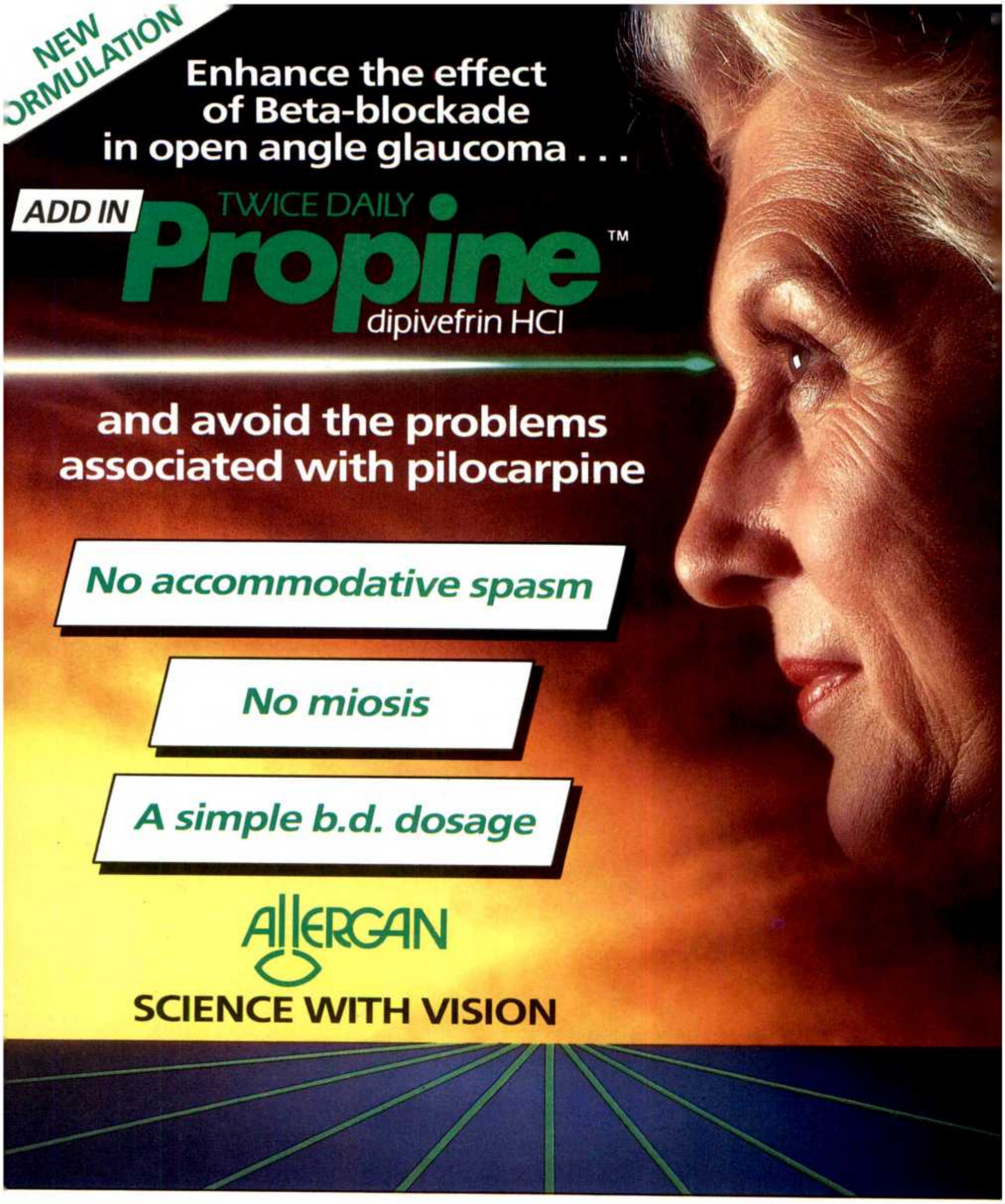

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British Journal of Ophthalmology, 1989, **73**, 333–336

Detection of HBs antigen, DNA polymerase activity, and hepatitis B virus DNA in tears: relevance to hepatitis B transmission by tears

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SUMMARY Hepatitis B surface antigen, DNA polymerase, and hepatitis B virus DNA have been sought in the tears of 72 patients. These markers were detected in a high percentage of hepatitis B carriers, which proves the presence of hepatitis B virus in the tears and raises the question of its eventual transmission in this way. The severity and extreme contagiousness of hepatitis B together with the increasing number of virus carriers justify systematic sanitary rules among ophthalmic clinicians and staff, but vaccination remains the best mean of limiting the spread of the disease.

The recent isolation of human immunodeficiency virus (HIV) from the tears of patients with acquired immune deficiency syndrome[1] or AIDS-related complex[2] made ophthalmologists aware of the possible transmission of virus diseases by those secretions The risk of hepatitis B transmission, however, may be much more important owing to its extreme contagiousness and the increasing number of chronic carriers. Hepatitis B epidemics are well known and rightly dreaded by workers in laboratories and blood transfusion and renal dialysis units, but ophthalmic clinicians are not alert enough to this risk and often neglect it, though it became evident when hepatitis B surface antigen (Hbs Ag) was detected in tears.[3-5] But this antigen, located on the virus envelope, is also found on non-infectious particles, so it remained possible that the virus itself did not infect the tears

Owing to a better knowledge of this virus and to the discovery of new markers of complete replicative forms it is now possible to confirm its presence in tissues or secretions. The aim of this study was to detect in the tears three markers of hepatitis B virus (HBV)—namely HBs Ag, DNA polymerase activity, and viral DNA (HBVDNA)—to analyse the risk of its transmission by ophthalmic patients, and to consider means of preventing that.

Material and methods

The tears of 72 patients were sampled by gentle pipetting, without conjunctival bleeding (which might alter the results). HBs Ag was detected in tears by an immunoenzyme method (Auszyme Monoclonal, Abbott Laboratories, North Chicago, Ill, USA), on 32 HBs Ag positive patients: five with acute hepatitis, 15 with active or persistent chronic hepatitis, and 12 asymptomatic carriers. Ten serum HBs Ag negative subjects were used as controls

DNA polymerase activity was sought in the tears of 20 HBs Ag positive patients with chronic hepatitis, 10 with high DNA polymerase serum levels, and 10 with insignificant levels. The dosage technique was based on Kaplan's method[6 7] and used the measurement of tritiated thymidine incorporation during DNA synthesis The enzyme specificity was evaluated by dosing its activity with phosphonoacetic acid, which does not inhibit HBV DNA polymerase, and with phosphonoformic acid, which inhibits it The difference between the two results gave the HBV-associated DNA polymerase value. Results were expressed in counts per minute (cpm). Increase in DNA polymerase activity has been defined as values exceeding 50 cpm.

HBVDNA was sought in the serum and the tears of 10 HBs Ag positive patients with chronic hepatitis by the spot hybridisation technique.[8 9] Tears and serum

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were placed on nitrocellulose filters which were hybridised with a radiolabelled ^{32}P DNA probe to detect the presence of HBVDNA. Results were obtained by autoradiography.

Statistical analysis was performed by Student's *t* test.

Results

HBs Ag was found in the tears of 21 out of 32 HbS Ag positive patient (Table 1)—namely, four of five with acute hepatitis (80%), 12 of 15 with chronic hepatitis (80%), and five of 12 asymptomatic chronic carriers (41%). The other 11 patients did not have detectable HBs Ag in the tears, though HBs Ag was detected in their serum. This group without detectable HBs Ag included two patients with dry eye from whom the collection of tears was somewhat difficult. The tears of the 10 HBs Ag negative controls were negative.

Abnormal DNA polymerase activity was detected in the tears of all the 10 chronic hepatitis patients with high serum levels of DNA polymerase (Table 2). Tear levels of DNA polymerase were lower than serum values, but the difference was not significant by Student's *t* test (t=1·533, 0·05<p<0·10). In one case DNA polymerase activity was higher in tears than in serum. In contrast, when DNA polymerase was negative in the serum (10 cases), no enzyme activity could be found in tears.

HBVDNA was detected in the serum of three out of 10 HBs Ag positive patients with chronic hepatitis. The tears of these three subjects were also positive for HBVDNA. At the time of the tear collection the other seven patients were negative for HBVDNA, both in serum and in tears. No correlation could be found between positivity for HBVDNA and serum DNA polymerase levels or severity of the chronic hepatitis, since one of the positive cases was considered to be persistent chronic hepatitis and presented negative serum DNA polymerase activity.

Table 1 *Detection of hepatitis B surface antigen in tears*

Acute hepatitis	*Chronic hepatitis*	*Asymptomatic carriers*	*HBs Ag negative controls*
4/5 (80%)	12/15 (80%)	5/12 (41%)	0/10 (0%)

Table 2 *DNA polymerase activity (cpm) of HBV in the serum and the tears of 10 HBs Ag positive patients with chronic hepatitis. Comparison of mean values obtained in serum and tears appears not to be significant (t=1·533, 0·05<p<0·1)*

Patients	Serum*	Tears*
1	296	176
2	1 164	570
3	751	512
4	1 669	1 528
5	1 317	960
6	10 210	10 752
7	8 111	6 094
8	311	162
9	290	191
10	112	79

*Negative values below 50 cpm.

Discussion

Though tears may transmit hepatitis B infection, studies of this subject are few.[1-4] Given the lack of a direct marker for the virus, only HBs Ag detection in tears could be taken as implying a risk of transmission in this way. Nevertheless, HBs Ag, which is a component of the HBV envelope, can also be found in serum and various secretions without infectious particles, so that the significance of its detection in tears may be doubted.

However, HBs Ag has been detected in only a few cases (30 to 50%), of acute or chronic hepatitis.[1 5] Till now it had not been found in the tears of asymptomatic carriers.[4] Our study confirmed in part the previous results on the detection of HBs Ag in tears but also showed the presence of the virus in tears owing to the use of specific markers, such as DNA polymerase, a replication enzyme associated with the nucleocapside,[8] and above all by the virus DNA itself.

Moreover, the high proportion of cases in which these three markers were detected in tears during HBV infection makes the risk of hepatitis B transmission much more important than was previously considered. In our study HBs Ag was found in 80% of cases of acute or chronic hepatitis and was also detected in the tears of asymptomatic carriers. It is the first report on the detection of HBs Ag in the tears of asymptomatic chronic carriers The discrepancies between our work and previous studies were probably due to the sampling method, as collecting the tears with Schirmer test strips may induce false negative results by absorption of numerous particles. Also noteworthy is the close correlation between serum and tears HBV markers, DNA polymerase and HBVDNA having always been found simultaneously in tears and blood.

As HBV markers were almost constantly present in the tears, all the virus carriers are potentially dangerous. The number of HBV carriers in the population, however, is very high—estimated at 0·5% in northern Europe, about 2% in southern Europe, and 15% in Africa and SE Asia.[11] To these must be added some HBV carriers with nondetectable HBs Ag levels.[12 13] The difficulty of detecting infectious subjects raises a real public health problem which ophthalmologists need to consider

Hepatitis B is a serious disease leading to death (1%) or to a chronic carrier state (10%), with frequent development of cirrhosis or hepatocarcinoma. It is highly contagious, the risk being estimated at 30% after pricking by contaminated material and even 90%[14] if the infected blood contains DNA polymerase or HBe antigen, which is another marker of viral replication.[15] Transmission is usually by blood and its derivatives,[16] rarely by secretions (saliva, semen, vaginal fluid, faeces, urine), through a cutaneous abrasion or an apparently healthy mucosa. A study by Bond *et al.* of hepatitis B infection by plasma inoculation on to the corneal surfaces of a chimpanzee,[17] and one case of transmission after accidental introduction of infected blood into the eye,[18] prove that the virus can be transmitted via the conjunctival mucosa or the cornea. Thus HBV infection could be carried from patient to patient by corneal or conjunctival transmission during tonometry, biomicroscopy, or contact lens fitting. HBV infection could be transmitted by this route if a tonometer or a contact lens was used first on an HBV carrier and then placed on a second patient's eye. A model for the spread of virus disease by tonometry exists in epidemic keratoconjunctivitis caused by adenovirus. The risk of HBV transmission through the cornea or the conjunctiva is supported by the previous detection of HBs Ag on a tonometer[3] and soft lenses[4] after contact with the eyes of an HBs Ag positive patient.

Tears, however, may also be dangerous for medical staff, and small cuts or scratches can provide a sufficient portal of entry through the skin for HBV to enter the body. DNA polymerase tear levels being very close to the serum values, the infectivity of tears is probably high. If a quantity as low as 0·1 µl of plasma can transmit the disease,[19] even small quantities of tears appear to be dangerous, so that strict sanitary rules should be followed. Particular care should be exercised if patients are known HBs Ag carriers or are considered to be at high risk of having this infection. High-risk patients include those undergoing renal dialysis, diabetics, drug addicts, and those who have received blood transfusion. However, a clearly indicative clinical context is not always present to warn the ophthalmologists that his patient may be a hepatitis B carrier, so that precautions should always be taken to prevent HBV transmission by tears.

Like HIV, HBV is sensitive to various disinfectants,[20] such as 80% alcohol and 5% sodium hypochlorite, but very high concentrations or temperatures are needed for its destruction All cleaning and sterilisation methods, however, can ensure efficient prophylaxis against patient-to-patient transmission of HIV and HBV, but are not sufficient to protect the medical staff completely. In practice HBV vaccination[21] appears to give the best protection, by injection of purified HBs Ag. Its efficacy rate reaches 95% after three injections at one-month intervals. It is well tolerated, and the technique avoids any risk of HIV transmission.

Nevertheless, the growing hepatitis B epidemic together with our detection of HBV in tears point to the risk of inadvertent HBV transmission by corneal transplantation. The only viral diseases reported to have been transmitted by corneal allograft are rabies[22] and Creutzfeldt-Jakob disease.[23] There is so far no clinical or serological documentation of transmission of HIV after corneal transplantation, though corneal allografts from HIV-seropositive donors have been described.[24] The Eye Bank Association of America, however, recently became aware of a case of possible hepatitis B infection via corneal transplant[25] and is now recommending HBs Ag screening for all potential corneal donors in addition to systematic HIV detection. HBs Ag identification in emulsified corneal tissue from one patient with acute hepatitis B[25] as well as HIV isolation from the cornea[26] support the need for screening of all corneal donors for HBs Ag and anti-HIV antibodies. If a corneal donor is found to be HBs Ag positive, the cornea should not be used for transplantation. If the results of HBs Ag screening are known after corneal transplantation, treatment of the recipient with hepatitis B immune globulins and HBV vaccine should be performed as soon as possible.

Thus the presence of HBV in tears raises problems of public health as well as HIV detection in these secretions. Even if prognosis for hepatitis B is less severe than that for the acquired immune deficiency syndrome, the disease must be taken seriously. The prevalence of HBV carriers and the extreme contagiousness of HBV infection constitute a real danger for ophthalmologists. HBV is not easy to destroy, but correct information together with systematic sanitary rules and more vaccination may help to limit the spread of this severe disease.

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Autosomal dominant retinitis pigmentosa: a log quotient analysis of the photopic and scotopic b-wave amplitude

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SUMMARY The relationship of the photopic and the scotopic b-wave amplitudes of the electroretinogram was studied in 85 normal subjects and 25 patients with autosomal dominant retinitis pigmentosa, in which one amplitude was at least 20 microvolts. The log quotient of their b-wave amplitudes—that is log of the photopic b-wave amplitude divided by the scotopic b-wave amplitude—was considered to represent the activity of cones relative to rods. The log quotient values had a normal gaussian distribution in the normal control eyes, while they formed two groups in the patients with autosomal dominant retinitis pigmentosa. In the first group (type 1), the scotopic b-wave was non-recordable while the photopic b-wave amplitude was larger than 20 microvolts in all cases, indicating that the log quotient is larger than 0·5 and that the rod system is much more severely affected than the cone system. The second group (type 2) had a log quotient smaller than 0·5 and its distribution almost overlapped the normal one, indicating more symmetrical damage in the cone and rod systems. The mean final rod threshold at 45 minutes for type 1 was significantly higher than that for type 2. The log quotient proved to be a useful index for analysing the cone and rod involvement and consequently provides a better understanding of autosomal dominant retinitis pigmentosa.

Retinitis pigmentosa (RP) is a group of disorders that are characterised by progressive visual field loss resulting from a degenerative process of the photoreceptor and pigment epithelial cell layers. Classification by genetic pattern is generally accepted.[1] However, it has been suggested that even within the same genetic pattern a heterogeneous disease process may exist.[2] Among genetic patterns autosomal dominant retinitis pigmentosa (ADRP) has been intensively studied by several investigators.[3-6] Their classifications, though determined by different examinations, are based on cone and rod involvement in the disease process and agree broadly on the point that ADRP (excluding sector RP) can be divided into two groups.

The cone and rod involvement in retinal disorders can be evaluated easily by amplitudes of the photopic and scotopic electroretinogram (ERG), which has been a routine method for evaluating RP patients.[1 7] In this study we propose the log quotient of the photopic b-wave amplitude (bp) divided by that of the scotopic b-wave (bs)—that is, log (bp/bs)—as a good indicator for assessing the cone and rod involvement in ADRP patients.

Subjects and methods

Eighty-five subjects (38 male and 47 female, aged 3 to 77 years) with normal ophthalmic findings were tested to study a normal distribution of the parameters. The mean (and standard deviation) of age for males and females were 31 (17) and 34 (20) years respectively, which were not significantly different.

For ADRP we selected 25 patients with recordable ERGs who had either photopic or scotopic ERG amplitudes larger than 20 μV with single flash techniques from a total of 89 consecutive ADRP

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Table 1 *Summary of clinical findings*

Case	*Age/ Sex*	*Onset of NB*	*Onset of VFL*	*Acuity*	*bp (μV)*	*bs (μV)*	*log (bp/bs)*	*bpt (ms)*	*DA*
Type 1									
415	16/F	15	UA	20/25	220	0	>0 5	36	1·0
416	24/F	1	24	20/20	80	0		44	4·2
634	45/F	14	UA	20/20	20	0		44	4·35
823	23/M	UA	UA	20/20	40	0		32	1 0
734	27/M	15	15	20/20	50	0		41	2 4
385	41/M	31	34	CF	20	0		54	4 8
849	40/M	34	34	20/25	90	0		44	5·0
355	44/M	UA	UA	20/20	30	0		48	1 15
417	20/F	1	17	20/30	70	0		46	4 5
646	19/M	8	16	20/25	100	0		46	2 4
86	32/F	24	UA	20/20	40	0		44	3·35
676	29/M	UA	UA	20/30	50	0		48	0·6
Type 2									
1023	37/F	32	32	20/30	40	20	0·301	42	2·4
644	50/M	30	30	20/20	110	80	0 138	32	3 15
754	31/M	21	UA	20/30	60	60	0	42	3 55
142	38/F	38	UA	20/20	150	160	−0 028	32	1·15
483	34/F	UA	UA	20/20	180	200	−0·046	34	ND
950	13/F	12	12	20/50	60	90	−0·176	40	ND
263	13/F	13	13	20/25	30	50	−0·222	40	0 5
523	34/F	UA	UA	20/30	50	110	−0 301	36	0 2
949	45/F	36	39	20/200	50	100	−0 301	42	2 0
1028	15/M	UA	UA	20/20	120	250	−0 319	32	1 0
1025	21/M	21	21	20/20	70	170	−0·385	35	0 5
1024	41/M	39	39	20/25	70	200	−0·456	34	2·1
468	29/M	9	24	20/25	10	50	−0 699	36	0 7

NB: night blindness, VFL: visual field loss, bp: photopic b-wave amplitude; bs: scotopic b-wave amplitude, bpt: photopic b-wave implicit time; DA final threshold of dark adaptation, CF: count fingers; UA. unaware of the symptom; ND: the test was not done

patients in the UCLA RP Registry. The clinical findings are listed in Table 1.

Full-field (Ganzfeld) ERGs with Burian-Allen contact lens electrode were recorded as described previously.[8] The scotopic ERG was recorded with a dim white flash (−1·58 log cd/m²/s) obtained by I-8 on Grass photostimulator (PS-22) and Kodak Wratten filter ND 2·0 after dark adaptation for 30 minutes or more. The photopic ERG with I-16 white flash (0·85 log cd/m²/s) was recorded in the presence of a steady 27·4 cd/m² background light. This method allowed recordings of 5 μV or more to be measured. Since responses from both eyes were symmetrical with few exceptions both in normal persons and RP patients, responses from the right eye of each subject were analysed except normal controls with retinal disease in the right eye.

The final threshold of dark adaptation was measured after 45 minutes of dark adaptation by Goldmann-Weekers adaptometer with a 1° test field located 12° below the red fixation light

Results

The distributions of bp/bs and the log(bp/bs) of normal control eyes are shown in Fig. 1. The histogram of bp/bs is asymmetrical, with its peak deviating towards the lower end, while the histogram of log(bp/bs) appears almost symmetrical. The cumulative percentage frequencies were plotted on probability paper in Fig. 2. The line for bp/bs curves up in the middle, while the line for log(bp/bs) appears almost straight, indicating that log(bp/bs) follows the normal gaussian distribution with a mean of −0·35 and a standard deviation of 0·11. There was no statistical difference between the values of log(bp/bs) in male and female (male: −0·33±0·12, female: −0·36±0·11). The scattergram of log(bp/bs) against age shown in Fig. 3 demonstrates no significant age effect (correlation coefficient −0·085).

In patients with ADRP, the log(bp/bs) for 13 patients out of 25 was distributed between −0·75 and 0·5, forming a single peak between −0·5 and −0·25

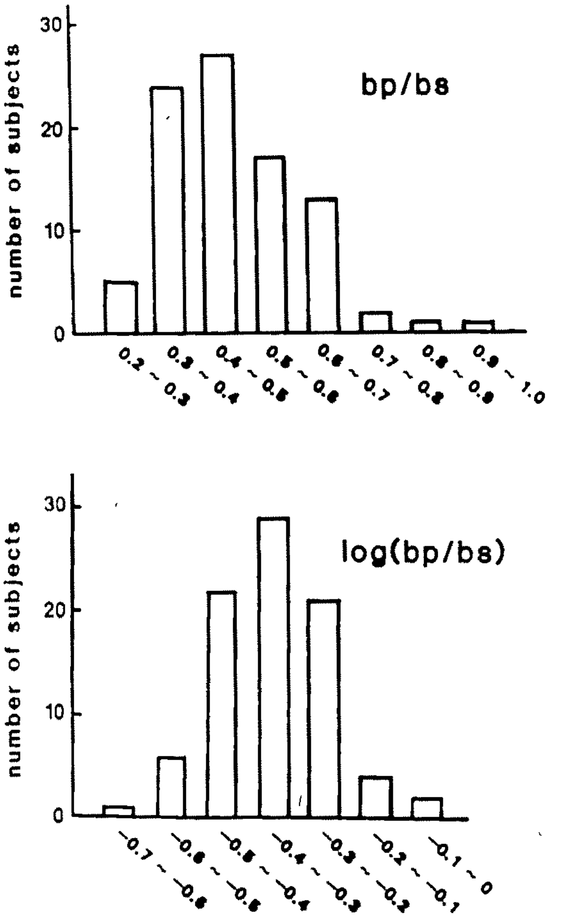

Fig. 1 *Histograms for bp/bs and log(bp/bs) of 85 normal control subjects. −0·7~means the individual log(bp/bs) fell within the range −0·7 to <0·06*

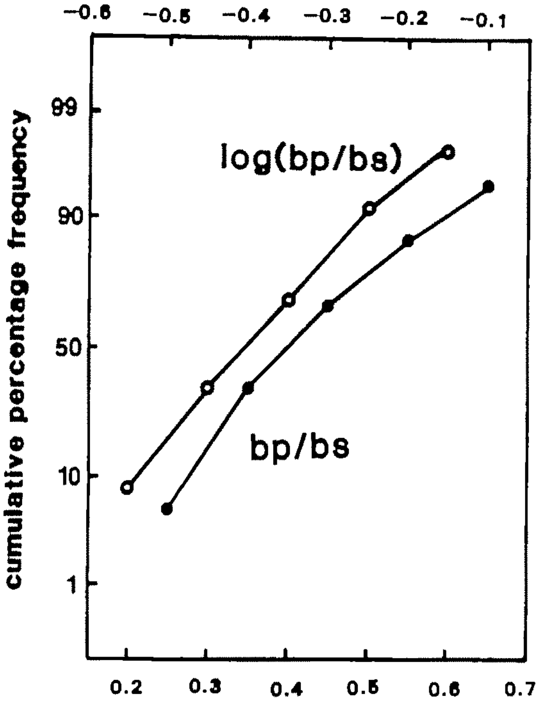

Fig. 2 *The cumulative percentage frequencies of the results in Fig. 1 expressed on a probability paper. The closed circles are for bp/bs; their values are shown at the bottom. The open circles are for log(bp/bs); their values are shown at the top.*

(Fig. 4). Although the 12 remaining patients showed unrecordable scotopic ERGs and thus their log(bp/bs) is unavailable, it could be estimated as larger than 0·5 because their unrecordable scotopic b-wave actually means less than 5 μV and the photopic b-wave in all cases was larger than 20 μV. Thus according to the value of log(bp/bs) all patients could be classified into two groups, namely, type 1 and type 2, with an arbitrary limit of 0·5. A summary of clinical findings of both groups is given in Table 2. Type 1 had higher final dark adaptation threshold values ($p \leq 0{\cdot}05$) and a more delayed photopic b-wave implicit time ($p \leq 0{\cdot}01$). More than one patient from each of three families were included in this study. Family No. 1 are cases 415, 416, and 417, family No. 2 cases 1023, 1024, 1025, 1028, and family No. 3 cases 949 and 950. All members of each family belonged to the same type.

Discussion

Cone and rod functions are evaluated by the photopic and scotopic ERGs respectively, and their amplitudes help the analysis of cone versus rod involvement in photoreceptor disease.[17] In general rod-cone and cone-rod degeneration are diagnosed on the basis of which system is predominantly involved.[18] When either the photopic or scotopic ERG is disturbed while the other shows a good response, the relative involvement of rods and cones is easily understood. But there have been no

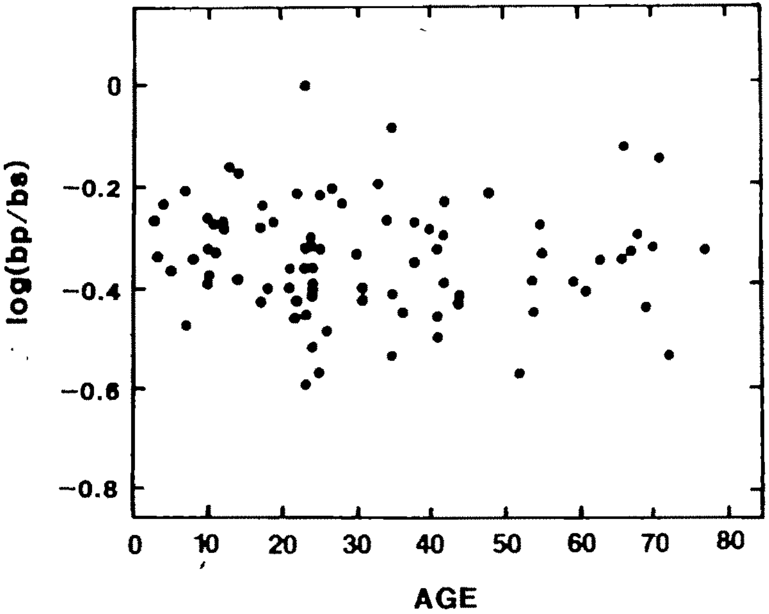

Fig 3 *Log(bp/bs) versus age in 85 normal controls.*

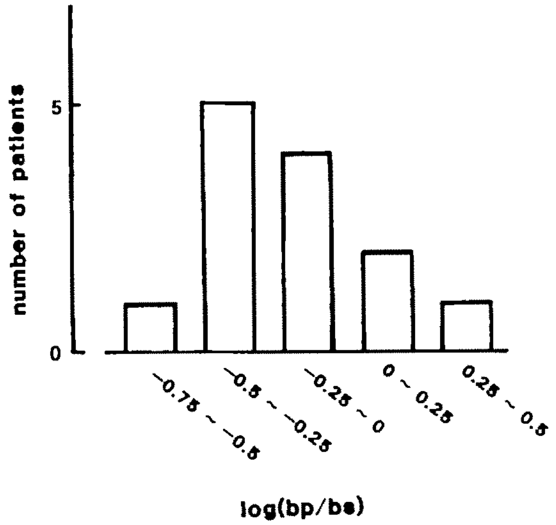

Fig 4 *Histogram for log(bp/bs) in patients with type 2 autosomal dominant retinitis pigmentosa*

reasonable criteria for determining predominant involvement of cones or rods when both photopic and scotopic b-wave amplitudes are decreased. We proposed a parameter of bp/bs for that purpose because it represents relative activity of cones compared with that of rods. A similar concept was introduced by Birch and Fish,[11] who recorded cone and rod responses with scotopically matched blue and red filters so that both amplitudes are equal in normal eyes, and defined cone-rod degeneration as having the quotient of rod/cone amplitude more than 1·0 But there was no reasonable basis to set a borderline at 1·0 and to subdivide RP patients at that point because there was no information about the distribution of this index in either the normal population of RP patients. Therefore we studied the distribution of bp/bs in normal eyes and ADRP patients.

Since normal eyes showed log normal distribution, log(bp/bs) is considered as a more reasonable parameter rather than bp/bs. The results from normal eyes also showed that log(bp/bs) neither differs significantly between male and female nor is correlated with age. These features are different from other ERG parameters such as amplitudes and implicit times, which are reported to be sex and or age dependent[12–14] and are thought to be advantageous as clinical parameters.

Table 2 *Clinical findings for type 1 and type 2*

	Type 1	*Type 2*
Number of patients	12	13
Age	30 (10)	31 (12)
Age at onset of night blindness	16 (11)	25 (11)
Photopic b-wave amplitude	68 (56)	77 (49)
Scotopic b-wave amplitude	0	118 (71)
Log(bp/bs)	<0·5	−0·19 (0·26)
Photopic b-wave implicit time	43·9 (5·7)	36·7 (4·0)**
Final threshold of dark adaptation	2·9 (1·7)	1·6 (1·1)*

Values are means (SD) *$p<0·05$, **$p<0·01$

The distribution pattern of log(bp/bs) in ADRP patients in this study clearly showed that ADRP patients can be divided into at least two subgroups, type 1 and type 2. Since the distribution in type 2 nearly overlaps the normal distribution, it could be said that their cones and rods are equally damaged, whereas in type 1 the rods are more extensively damaged.

Type 1 and type 2 were different in the degree of final threshold elevation and in the delay of the photopic b-wave implicit time, with greater delays in type 1. The difference in age at onset of night blindness between the groups was not significant, which might be owing to the relatively small number of subjects. This finding is in marked contrast to the results of Lyness *et al.*,[5] where age of onset correlated with type. Their selection of types was based on psychophysical testing, while our group is based on electrophysiological results. Since data for age at onset represent subjective reporting by the patient and are influenced by variant living conditions, differences in age of onset are not surprising The lack of intrafamilial variation is strong evidence in support of our classification.

There have been several reports on RP subclassification. Marmor[15] showed that RP patients with normal cone implicit time have a better visual prognosis than those with prolonged cone implicit time irrespective of their inheritance pattern, and called this group of patients 'delimited RP'. Type 2 patients in our classification had significantly less delay in photopic b-wave implicit times than type 1 patients. Since cone implicit times are related to amplitudes of the photopic b-wave and the scotopic b-wave,[16] which are subject to progression of the disease process, it is not certain whether cone b-wave implicit times can render a substantial subclassification of RP types, and good serial ERG studies will need to be performed in the delimited RP group to substantiate this point.

Arden and colleagues[3] defined two subgroups in ADRP based solely on the presence or absence of the scotopic ERG. Their subgroup A, in which no scotopic ERG was evoked, broadly (though not exactly) corresponds to our type 1, and their subgroup B, in which the scotopic b-wave is present, to our type 2. Considering the progressive nature of ADRP, patients in their subgroup A could have had recordable scotopic ERGs in early stages, and those in subgroup B should lose the scotopic ERG in a very advanced stage. This problem may have also influenced our study, though the methodology helped to minimise it.

There have been attempts to subclassify ADRP by psychophysical techniques. Massof and Finkelstein[4] defined two types of ADRP—type 1 with early diffuse loss of rod sensitivity and later loss of cone sensitivity, and type 2 with a regionalised and combined loss of rod and cone sensitivity. Lyness and associates[5] proposed a similar subclassification on the basis of a two-colour automated static perimeter. In their subgroup D severe and diffuse loss of rod function is shown with patchy loss of cone function. In their subgroup R loss of rod function is regional and accompanied by loss of cone function.

These psychophysical methods for subclassification are reasonable, but unfortunately the methods have not become a part of the routine clinical examination, and standardisation among research centres is not easy. Our classification by log(bp/bs) is an objective method and can be used wherever electroretinographic studies of RP patients are performed in which the cone and rod systems are measured separately.

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Ten-year experience with primary ocular 'reticulum cell sarcoma' (large cell non-Hodgkin's lymphoma)*

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SUMMARY Fourteen patients with intraocular 'reticulum cell sarcoma' (non-Hodgkin's large cell lymphoma) ranging in age from 27 to 77 are presented. All patients had evidence of vitritis with 50% showing intraretinal and/or subretinal lesions and 21% having anterior uveitis. Five of the patients developed central nervous system lesions and subsequently died. Primary radiation therapy to the eyes and CNS appears to prevent spread of the disease and improve longevity. Chemotherapy improved survival in one patient with CNS spread of disease.

Reticulum cell sarcoma (RCS) is a rare non-Hodgkin's large cell lymphoma which can masquerade as chronic uveitis. This disease occurs in two broad forms, with one variety primarily involving the systemic lymph nodes, visceral organs, and uveal tract and another primarily affecting the retina, vitreous, and central nervous system (CNS). In the Rappaport classification the disease was relabelled as a histiocytic lymphoma.[1] More recently surface marker studies[2] have shown these cells to be of lymphoid and not histiocytic origin.

Over 100 cases[3-10] of ocular RCS have been described in the literature. Typically, the patients have been in their sixth or seventh decade when either a unilateral or bilateral painless decrease in visual acuity occurred. No sexual or racial prediliction has been noted. Invariably, ocular findings include vitreous cells and debris (Fig. 1). The retina and choroid (Fig. 2), the conjunctiva, and the optic nerve may be infiltrated by tumour. Less commonly an anterior chamber reaction or an exudative retinal detachment may be presenting sign (Fig. 3). Systemic spread is common, with the CNS being affected first (Fig. 4). It is not clear if this spread of tumour represents true metastatic disease or whether it reflects a multicentric origin of the lymphoma. Diagnosis is achieved by means of vitreous aspiration and examination of a slide prepared from the cytospin or Millipore filter of the specimen (Fig. 5).

Over the last 10 years we have had the opportunity to treat 14 patients with RCS, with a follow-up time of up to seven years. A profile of these patients, their clinical findings, and treatment is presented (Table 1).

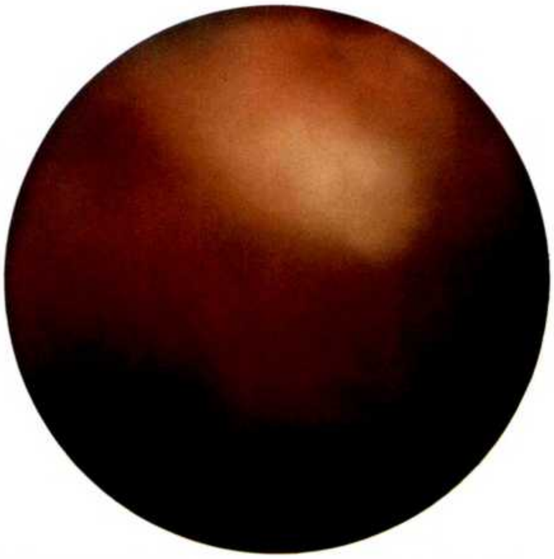

Fig. 1 *Vitritis and subretinal lesions in patient with active disease.*

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*Presented at the annual meeting of the American Academy of Ophthalmology in Dallas, Texas on 11 November 1987.

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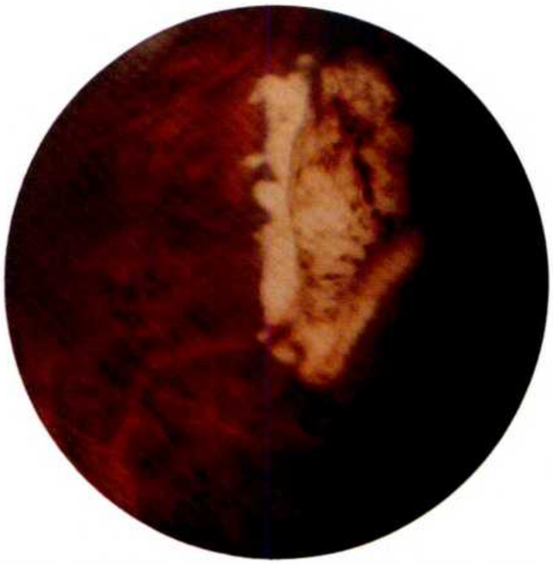

Fig. 2 *Large subretinal nodule seen at initial presentation.*

Results

The age at presentation ranged from 27 to 77 years, mean 65. Nine out of 14 or 64% of the patients were women, with no black patients in our series. Disease was bilateral in 71% of the patients. There was vitritis in 100% of the patients and retinal/subretinal lesions in 50%. Three of the fourteen patients had an anterior uveitis as well, with one being moderately intense.

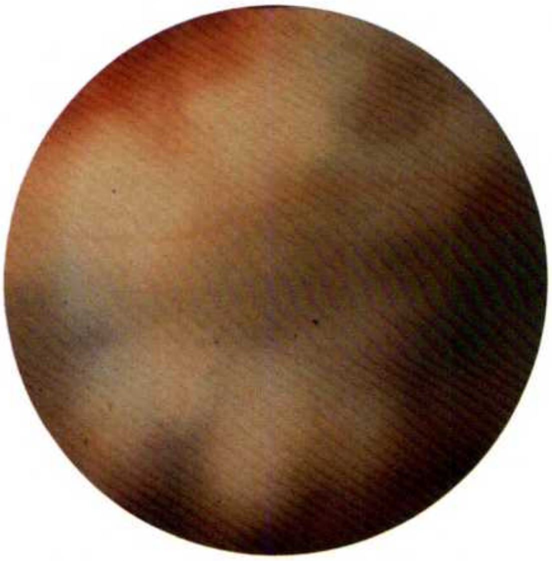

Fig. 3 *Extensive vitritis and exudative detachment as presenting sign.*

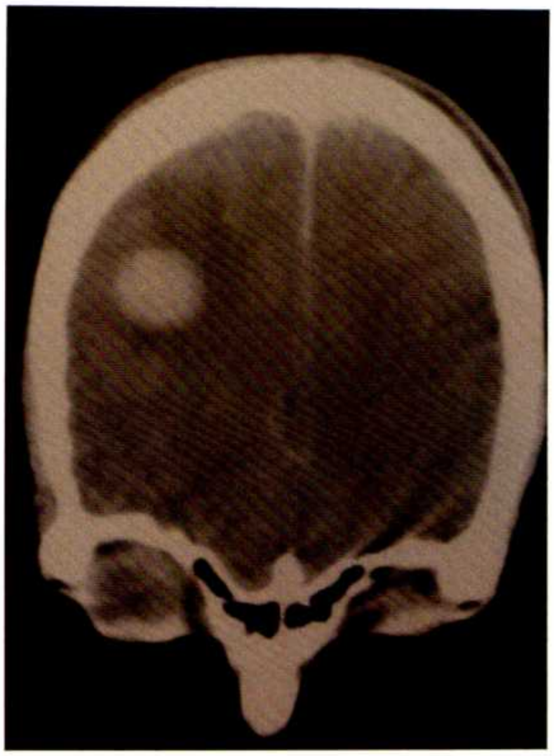

Fig. 4 *Typical CNS lesion from metastatic RCS.*

Initial investigations included a complete systemic evaluation with head CT scan, lumbar puncture for examination of cerebrospinal fluid, and bone marrow aspiration. Central nervous system involvement was present at the time of initial diagnosis in two cases and subsequently developed in four additional patients. All patients with CNS lesions except one died about six months after the presence of these lesions was confirmed.

The diagnosis of RCS was confirmed in 11 patients by means of a vitreous aspiration. This was performed with a 19 gauge needle introduced via the pars plana with 0.5 ml of fluid aspirated. One patient refused any diagnostic or therapeutic manoeuvres and two patients were not suspected of harbouring RCS until the time of necropsy. Nine patients who were diagnosed by vitreous aspiration underwent radiation therapy. Of the two patients who received radiation only to the orbits and not the brain one subsequently developed CNS lesions. One patient who received CNS and orbital radiation had an ocular recurrence after one year and systemic recurrence 18 months after initial diagnosis (Fig. 4) but was without evidence of CNS spread. In an additional

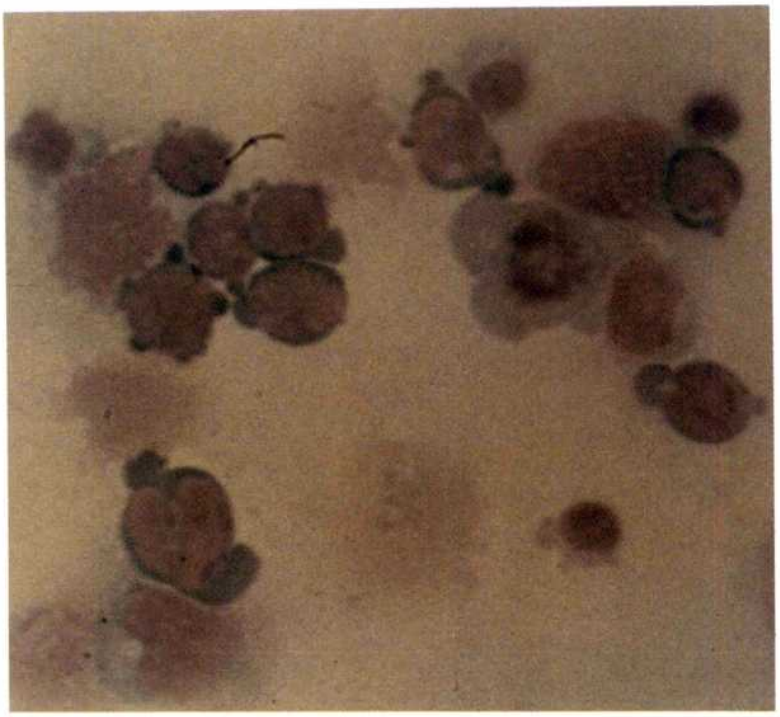

Fig 5 *High-power view of vitreous cytospin showing the large atypical cells seen in large cell lymphoma. Giemsa, ×1200.*

patient an ocular recurrence and a new brain lesion appeared one and one-half years after ocular and CNS radiation.

In patients who received primary radiation therapy, chemotherapy was reserved for recurrent CNS disease and was effective in one case in causing regression of tumour and preventing death. Two patients received intravenous cytosine arabinoside (Ara-C) as primary therapy for localised ocular disease. At three months follow-up there was no evidence of metastatic disease and partial improvement in ocular findings, though visual acuity remained unchanged.

Our chemotherapy protocol was to give Ara-C 2000–3000 mg/m^2 intravenously over a period of one hour. Treatment was repeated every 12 hours for three doses in the hospital and then as single doses repeated at weekly intervals as an outpatient. Toxicity was minimal, consisting of nausea, vomiting, and myelosuppression. No patients showed signs of CNS or cerebellar toxicity.

Discussion

Our findings confirm many of those noted in smaller series of cases of RCS. Although the mean age of 65 in our series is similar to that in previous reports, one patient was 27 at initial diagnosis. Interestingly, the first patient described with RCS was also 27[11] and so emphasises that, though very unusual, this condition should be thought of in younger patients as well as the elderly.

The most frequent finding in this series was an unexplained posterior and occasionally anterior uveitis. While negative blood studies, chest *x*-ray, and a thorough retinal examination can help to exclude some causes of uveitis, a vitreous aspiration is required for definitive diagnosis. This procedure was performed in all of our patients who consented and in whom the diagnosis was suspected. When present, a characteristic funduscopic picture of multicentric subretinal pigment epithelial lesions[12 13] can help suggest the diagnosis of RCS and was present in half our cases.

Tissue typing is useful in systemic lymphomas both for prognosis and in guiding therapy. Determining whether our cases of RCS were of B-cell or T-cell origin was very difficult given the small volume of vitreous aspirate obtained in individual cases. Only one patient could be typed and this patient had a T-cell lymphoma. Other workers have noted a predominance of B-cell lymphomas,[14] but all involve a small number of cases. Whether this information will become useful in future in planning treatment of RCS remains to be determined. It is possible that a pars plana vitrectomy would facilitate typing by providing

Table 1 *Data summary of patients with reticulum cell sarcoma seen over the last 10 years*

Age/sex	*Initial visual acuity*		*Ocular findings at presentation*	*CNS lesions at presentation*	*Radiation treatment*	*Chemotherapy*	*Recurrence*	*Outcome*	*Length of follow-up*
	OD	*OS*							
55/F	20/20	20/25	Vitreous cells, OS	Yes	40 grey (4000 rad) brain and OS	Cytoxan, adriamycin, prednisone, vincristine (used after recurrence)	CNS lesions	Died 1½ yr	
60/F	20/30	20/25	Vitreous cells OU	None	40 grey brain and OU	None	None	Visual acuity unchanged, no metastases	6 mon
27/F	20/15	20/50	Vitreous cells, OU, focal area of RPE atrophy OS	None	40 grey brain and OU	IV Ara-C after recurrence	CNS after 1½ years	20/20 OU, metastases improved with Ara-C	18 mon
66/F	20/50	20/40	Vitreous cells and posterior vitreous detachment OU	None	40 grey brain and OU	None	None	20/30 OU	9 mon
55/F	20/70	20/20	Anterior uveitis OU, Koeppe nodule OD, retinal masses/infiltrates OD, vitreous cells OU	None	4000 rad brain and OU	None	None	20/20 OU; required low dose oral prednisone for mild persistent uveitis. Repeat vitreous tap normal 1 year ago	3½ yr
70/M	20/200	20/200	Vitreous cells OU	None	40 grey OU	Methotrexate, adriamycin, prednisone (used after recurrence)	CNS lesions in 6 months	Lost to follow-up, visual acuity 20/70 OD and 20/400 OS, CNS lesions still present and patient gravely ill	2 yr
64/F	20/70	20/200	Vitreous cells OU, cystoid macular oedema and retinal exudates OS	None	20 grey OU	None	None	20/20 OD, 20/70 OS, no metastases or large bowel involvement	7½ yr
70/M	20/70,	Finger counting	Vitreous cells OU, retinal exudates OS	None	40 grey brain and OU	None	Ocular, and large bowel involvement, 1 year. No CNS lesion	20/80 OD, 20/100 OS, terminally ill	1½ yr
61/M*	20/30	20/30	Vitreous cells OU	None	Refused	Refused		Died 6 months with CNS disease	·
68/M	20/30,	Finger counting	Coarse vitritis OD, retinal exudates OS	None	40 grey brain and eyes	None	None	20/30 OD and 20/50 OS	1 yr
66/M*	20/400	20/40	Trace anterior uveitis OU, sub–retinal lesions OS, vitreous cells OU	None	None	40 mg prednisone p o. qD		Died after 6 mon Diagnosed post mortem	
77/F*	20/30	20/200	Vitreous cells OU, retinal exudates OS	None	None	40 mg prednisone orally as required		Died after 6 mon Diagnosed post mortem	
66/M	20/20	20/50	Vitreous cells OS	None	None	IV Ara-C	None	Acuity unchanged	3 mon
62/F	20/30	20/100	Trace anterior uveitis OS 4+ vitreous cells OS	None	None	IV Ara-C	None	Acuity unchanged	3 mon

*Cases previously reported [4]

a larger quantity of cells than is obtained by vitreous aspiration.

The rapid demise of all patients who developed central nervous system lesions speaks for the need to prevent spread of this rapidly fatal disease. Radiation therapy causes effective amelioration of ocular symptoms and was usually given in a dosage of 40 grey (4000 rad). Although largely empirical, whole brain radiation of 40 grey was also given in the hope of preventing CNS spread of disease. Within the limitations of our follow-up only one patient who was free of CNS lesions at presentation and received prophylactic whole brain radiation subsequently developed CNS metastasis. One additional patient developed systemic but not CNS spread of disease. This contrasts with a 75% incidence[15] of CNS involvement reported in other series. Our radiation protocol is similar to that used in other centres.[16]

The use of chemotherapy for RCS is less clear. The experience of Char *et al.*[17] with three patients given combination chemotherapy, including intrathecal treatment, was favourable. Baumann *et al.*[18] successfully treated one patient with intravenous high-dose cytosine arabinoside (Ara-C) who suffered recurrence after radiation therapy. Evidence suggests that Ara-C reaches therapeutic levels in the CSF and vitreous after intravenous therapy.[18] Our experience with three patients given high-dose intravenous Ara-C has been encouraging. Our one patient with the best response had received radiation therapy primarily. A prospective trial to evaluate the role of systemic high-dose Ara-C in combination with ocular and CNS irradiation as primary therapy needs to be undertaken.

In summary, a high degree of suspicion is needed in patients in whom a chronic posterior uveitis of obscure aetiology persists. Chronic uveitis is unusual in people over 60, and the differential diagnosis includes sarcoidosis, syphilis, tuberculosis, toxoplasmosis, Whipple's disease, cytomegalovirus infection, metastatic disease, and amyloid disease. The presence of multifocal subretinal lesions is even more suggestive of RCS. If the diagnosis of RCS is entertained, diagnosis can easily be confirmed by means of a vitreous aspiration. It should be remembered that young patients may occasionally be affected with this disease as well. It seems reasonable that such patients with idiopathic posterior uveitis with or without characteristic fundus lesions should undergo diagnostic vitreous aspiration.

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Lacri-Lube Prescribing Information. Presentation: Sterile, bland, non-medicated ophthalmic ointment for topical administration to humans, containing white petrolatum mineral oil, non-ionic lanolin derivatives with chlorobutanol 0.5% as a preservative. **Uses:** Useful as adjunctive therapy to lubricate and protect the eye in conditions characterised by exposive keratitis, decreased corneal sensitivity, recurrent corneal erosions, and keratitis sicca. **Dosage and administration:** For topical administration. Pull lower lid down to form pocket. Apply small amount as needed. **Contra-indications etc:** No known contra-indications. **Pharmaceutical precautions:** Store away from heat. To avoid contamination during use, do not touch tip to any surface. **Legal Category:** P. **Package quantities:** Available in 3.5g ophthalmic tubes. **Basic NHS Cost:** (as at May 1987) £1.76. **Product Licence Number:** PL 0426/0041. **Product Authorisation Number:** PA 148/38/1 (Allergan Pharmaceuticals (I) Limited, Westport, Co Mayo).

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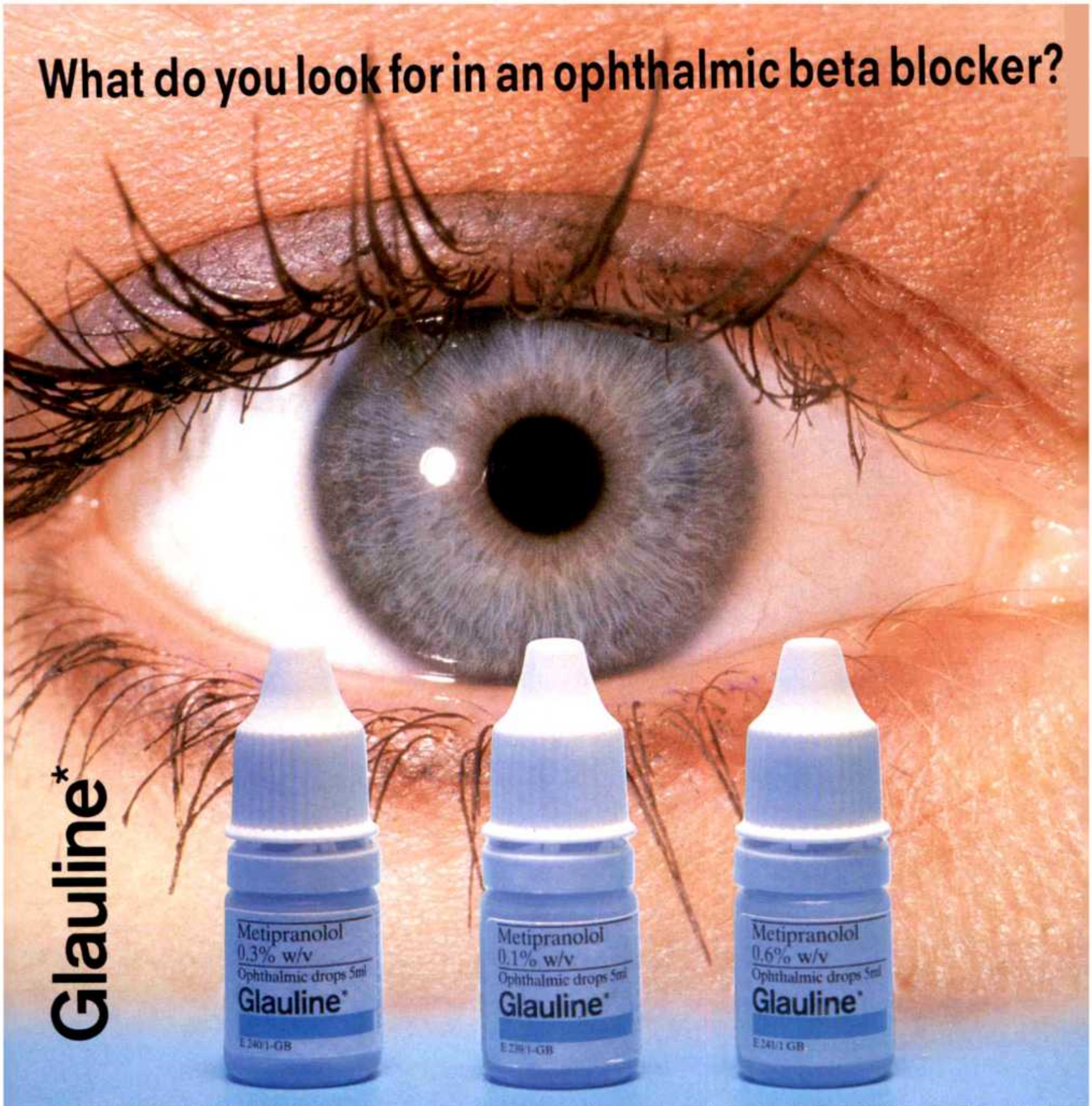

PRESCRIBING INFORMATION

PRESENTATION

A clear, colourless solution in a plastic dropper bottle. Glauline is available in three strengths containing 0.1%, 0.3% or 0.6% w/v metipranolol together with benzalkonium chloride 0.01% w/v as a preservative.

USES

Glauline is a beta adrenoceptor blocking agent used in the topical treatment of chronic open-angle glaucoma and other conditions in which intra-ocular pressure is elevated above normal levels.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop instilled into the affected eye twice daily. Newly diagnosed patients should be treated in the first instance with Glauline 0.1%, changing to a higher strength if adequate control is not achieved or maintained. Patients on existing therapy, whether or not this is to be continued, should receive 0.3% Glauline and the intraocular pressure of all patients should be monitored regularly (e.g. every 4-6 weeks).

Use of the 0.6% strength is only recommended in patients who are not controlled on the lower strengths of Glauline.

CONTRA-INDICATIONS, WARNINGS ETC.

The use of Glauline is not recommended in patients with obstructive airway disease, cardiac failure or hypersensitivity to metipranolol. Beta blockers should not be given with verapamil and neither drug should be administered within several days of discontinuing the other. As absorption into the circulation is possible, Glauline should only be used with caution in patients already receiving similar drugs by mouth. In particular, care should be taken in patients with sinus bradycardia and greater than first degree heart block. Although there is no evidence to suggest that metipranolol has teratogenic properties, its use during pregnancy should be avoided, unless the potential benefits are considered to outweigh the possible hazards. No clinical trials in children have been carried out. Glauline should not be used in patients fitted with soft (hydrophilic) contact lenses.

PHARMACEUTICAL PRECAUTIONS

Glauline should not be diluted or dispensed from any container other than the original bottle. It is potent for three years unopened, but as with other eye drops the contents of each bottle should be discarded one month after opening.

LEGAL CATEGORY – POM

PACKAGE QUANTITIES

Glauline is supplied as a sterile ophthalmic solution in a 5ml plastic dropper bottle.

FURTHER INFORMATION

Glauline has little or no effect on pupil size or accommodation. Glauline is generally well tolerated but some patients may complain of a slight stinging which soon passes off. Transient headaches have also been reported.

PRODUCT LICENCE NUMBERS

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Product Licence Number: PL 0426/0009R. **Date of preparation:** July 1988. **Reference:** 1. Bron AJ. Trans Ophthalmol Soc U.K. (1985); **104:** 801-826.

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British Journal of Ophthalmology, 1989, 73, 347–353

Benign hair-follicle derived tumours in the differential diagnosis of basal-cell carcinoma of the eyelids: a clinicopathological comparison

W SIMPSON, A GARNER, AND J R O COLLIN

From Moorfields Eye Hospital and the Institute of Ophthalmology, London

SUMMARY Benign eyelid tumours derived from hair follicles are rare and frequently misdiagnosed as basal-cell carcinoma when evaluation is based on clinical evidence alone. They include trichoepithelioma, trichofolliculoma, trichilemmoma, and pilomatrixoma. We reviewed 117 such tumours received in the Department of Pathology, Institute of Ophthalmology, London, in the last 30 years, a number which compared with 2447 basal-cell carcinomas seen over the same period. The hair follicle tumours may be safely excised with a narrow margin of clearance, whereas a macroscopic clearance of 3 to 5 mm or surgery with frozen section histological control is desirable for excision of basal-cell carcinoma. Therefore confirmation by incisional biopsy of the nature of any large lesion suspected of being a basal-cell carcinoma is essential in order to avoid performing an unnecessarily extensive or time consuming excision.

Basal-cell carcinoma (BCC) of the eyelid is the commonest malignant neoplasm in this situation, and its surgical excision was described as long ago as 1755 by Daviel.[1] Effective management requires scrupulous attention to the completeness of removal, and frequently this means excision with generous margins. Conversely, the much rarer benign tumours of hair follicle origin affecting the eyelid may be safely excised with a narrow margin of clearance. But because, perhaps, of their relative rarity or occasional clinical similarity to BCC such tumours can be either overlooked or confused in differential diagnosis and the patients may be subjected to unnecessarily extensive surgery.

The purpose of this paper is to review the pathology of the various types of benign hair follicle tumour, with particular reference to specimens received in the Department of Pathology, Institute of Ophthalmology, London, over the last 30 years and to illustrate the potential for clinical misdiagnosis from cases passing through Moorfields Eye Hospital.

Trichoepithelioma

Histopathology. The characteristic finding is the presence of multiple horn cysts containing concentrically laminated keratin or a less structured hyaline material (Fig. 1). The cysts lie within the dermis surrounded by a mantle of cells similar to those seen in BCC (Fig. 2), and these cells are frequently arranged in a reticulate manner. Calcification may be seen within the horn cysts, as may a surrounding foreign-body reaction. The usual trichoepithelioma is a nodular lesion, but a desmoplastic variant, which accounts for about 13% of all such tumours, is also described[2] in which clumps of epithelial cells are enveloped by prolific dense fibrous tissue (there is no artefactual separation between the epithelial growths and the stroma as is commonly observed in BCC).

The face is a common site for trichoepitheliomas to present. Some 83% of nodular lesions[3] and almost all desmoplastic tumours[4] occur in this situation, but reports in the literature refer to a single example of each variant involving the eyelids alone.[4,5] Gray and Helwig[3] reported just one eyelid tumour in a series of 83 solitary trichoepitheliomas, and Aurora and Blodi[6] found no eyelid trichoepitheliomas in a series of 678 benign eyelid lesions. Analysis of our own material has revealed 18 cases meeting the histological criteria for such a diagnosis, all of which were of the nodular type. Whether the absence of the desmoplastic variant in the eyelid is significant is

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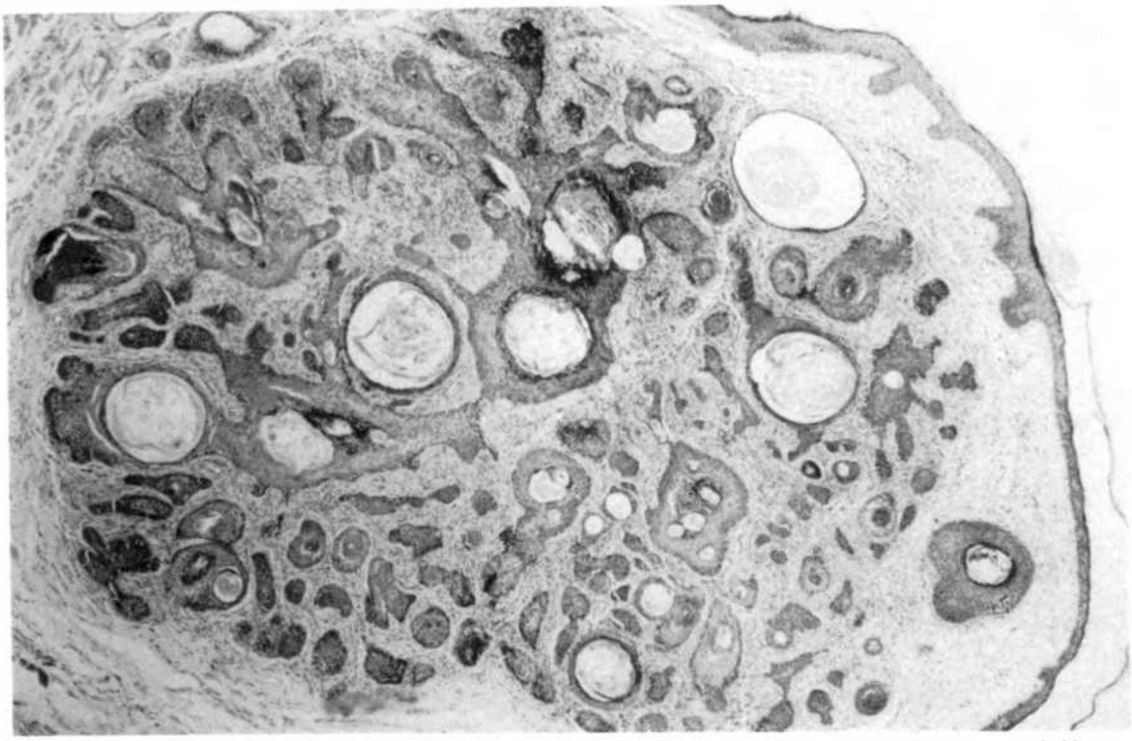


Fig. 1 *Trichoepithelioma. A fairly circumscribed nodular tumour consisting of multiple keratinous cysts surrounded by proliferating epithelium is seen within the dermis of the eyelid. (Haematoxylin and eosin, ×45.)*

doubtful, especially as the possibility that some such tumours were misdiagnosed as morphoeic BCC cannot be excluded. Although the tumours reviewed by us occurred over a wide age range of 3 to 73 years, presentation before the age of 30 years was unusual and the mean was 46·8 years. In respect of the youngest patient the tumour was thought to have been present from birth. There were 12 male and six female patients in our series.

In cases where the location was known both sides were equally affected, and the upper lid was involved twice as frequently as the lower. It was exceptional for the tumour to arise from the medial canthus, and there was no instance of lateral canthus involvement.

Two of the patients suffered recurrences after 10 and 12 years, but continuing follow-up, covering the next 15 and 14 years respectively, has not been associated with further recurrence.

In the skin, in general, trichoepithelioma may occur as multiple nodules, inherited in an autosomal dominant manner and presenting at about puberty (Brooke's tumour) in association with multiple familial adnexal tumours,[7-9] blue naevi,[10] or epidermal naevi.[11] Alternatively the tumour may be sporadic and solitary, presenting as an asymptomatic, flesh-coloured nodule which grows very slowly to attain a maximum diameter of about 5 mm. Such neoplasms may present at any age but are most common in young women.[2 3]

ILLUSTRATIVE CASE HISTORY

This is a case of a patient with a trichoepithelioma initially diagnosed as BCC. A 73-year-old Caucasian male normally resident in a sunny subtropical country presented with a three months history of a rapidly growing encrusted lesion of the skin of the lateral part of the lower eyelid and adjacent cheek (Fig. 3). There was no enlargement of regional lymph nodes. The tumour measured 25×20 mm, and was ulcerated and haemorrhagic. A clinical diagnosis of BCC was made, but diagnostic biopsy showed it to be a trichoepithelioma. Subsequently the tumour was excised, with a narrow margin of clearance, and a postauricular whole thickness skin graft was placed to close the defect. The lesion has not recurred in a six-month follow-up period.

Trichilemmoma

Histopathology. The affected cells arise from the

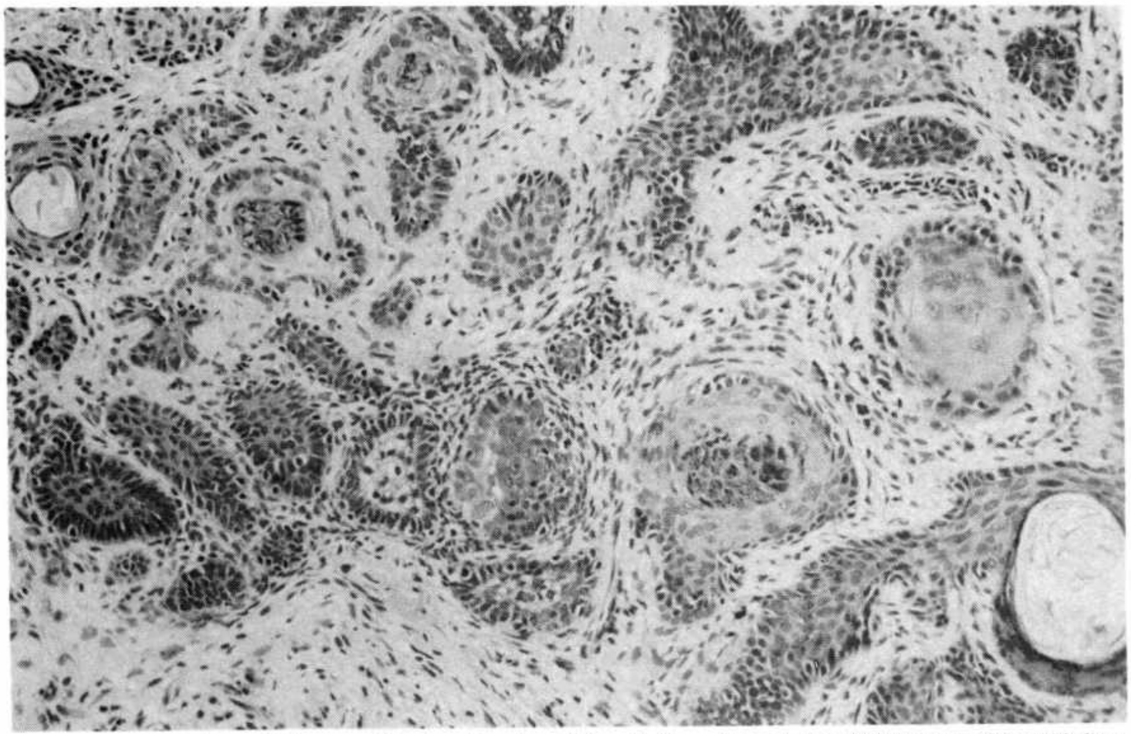


Fig. 2 *Trichoepithelioma. Higher magnification of another trichoepithelioma shows the basaloid character of the epithelium in the form of darkly stained cells and marginal palisading. Attempted hair follicle formation is also seen. (Haematoxylin and eosin, ×180.)*

outer layer of the hair sheath and as such are rich in glycogen. They proliferate to form acanthotic lobular masses within the dermis and a frequent palisading of the cells at the periphery of each lobule can simulate a BCC (Fig. 4). The basement membrane surrounding the lobules is often thickened (Fig. 5), and one or more hair follicles are usually present. We have seen four examples of this type of tumour involving the eyelid.

Clinically trichilemmoma presents as an asymptomatic, slowly growing, small reddish or yellow nodule and is most common in patients in the sixth decade. Hidayat and Font,[12] who described a large series of patients with trichilemmoma of the eyelid and eyebrow, commented that some of the tumours were misdiagnosed both clinically and, less often, histologically as BCC. Even more frequent clinical misdiagnoses were verruca and cutaneous horn.

ILLUSTRATIVE CASE HISTORY

A 46-year-old Caucasian male presented with a small lump measuring up to 3 mm across at the margin of his left lower lid. The lesion had been present for one year and had bled. A clinical diagnosis of BCC was made but a full thickness excision biopsy showed it to be a trichilemmoma. There has been no recurrence over a nine-month period.

Pilomatrixoma

Histopathology. The tumours are located in the

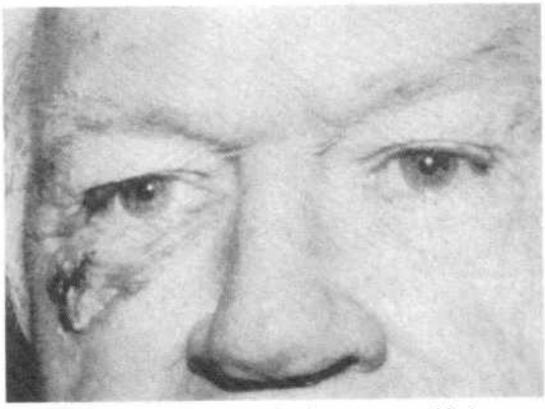


Fig. 3 *Trichoepithelioma. This large encrusted lesion affecting the right lower eyelid and adjacent cheek was originally considered to be a basal-cell carcinoma.*

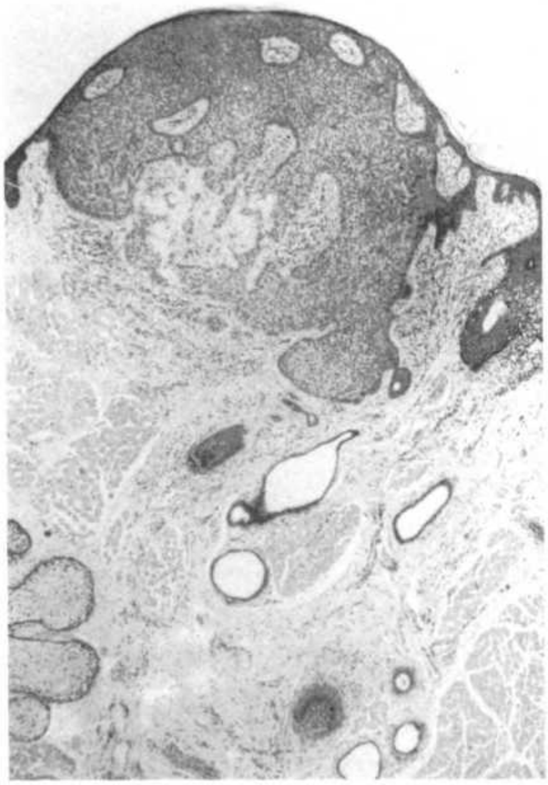


Fig. 4 *Trichilemmoma. A solid mass of proliferating epithelium is seen extending into the dermis of the lid with palisading of the cells at the periphery of the downgrowths. (Haematoxylin and eosin, ×34.)*

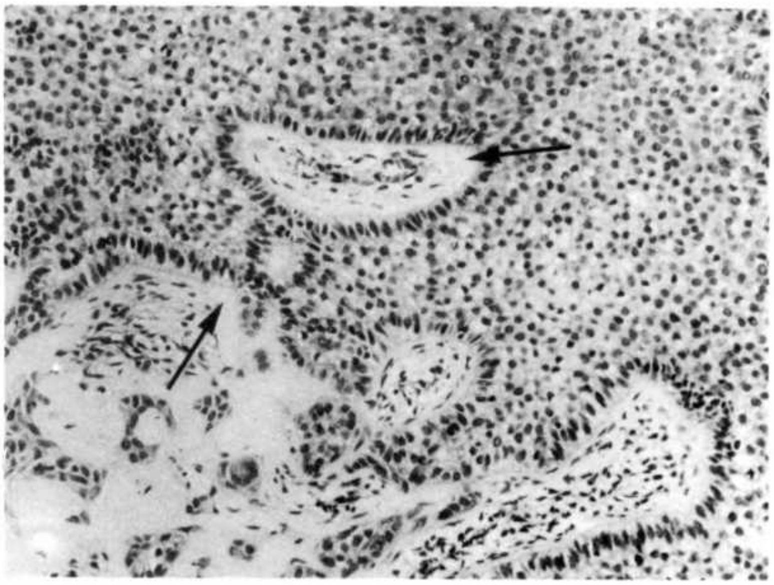
dermis and are well demarcated. Large masses of strongly basophilic epithelial cells reminiscent of basal cells merge with areas in which the cells are reduced to ghost outlines with barely distinguishable nuclei. Calcification is common in these latter areas, and a foreign-body giant cell reaction is often seen in the fibrous tissue stroma of the tumour (Figs. 6, 7). An incomplete capsule is often seen.

Pilomatrixoma, which is alternatively referred to as calcifying epithelioma (of Malherbe), can occur at any age although over the skin as a whole some 60% present within the first two decades.[13] The upper lid and eyebrow are favoured sites,[14 15] and they constitute about 1% of all childhood eyelid lesions.[16] They normally present as very slowly growing, small, hard, solitary nodules beneath normal epidermis.[17] Largely because of the age difference at the time of presentation, misdiagnosis of pilomatrixoma as BCC is uncommon, though we know of one instance in which BCC was the preferred clinical diagnosis.

ILLUSTRATIVE CASE HISTORY

A 29-year-old Caucasian male presented with a nine-month history of a rapidly growing lump involving the right lower eyelid and adjacent cheek (Fig. 8). It measured 30 mm in diameter, was tender, encrusted, and had bled. There were no palpable regional lymph nodes. A differential diagnosis of BCC, followed by squamous-cell carcinoma and keratoacanthoma, was entertained before incisional biopsy showed the tumour to be a pilomatrixoma. The lesion was subsequently excised with a narrow margin of clearance, and the defect was repaired with a post-

Fig. 5 *Trichilemmoma. The epithelial proliferation shows marginal palisade alignment, more centrally placed clear cells and a conspicuous basement membrane zone between the epithelium and stroma (arrows). (Haematoxylin and eosin, ×144.)*



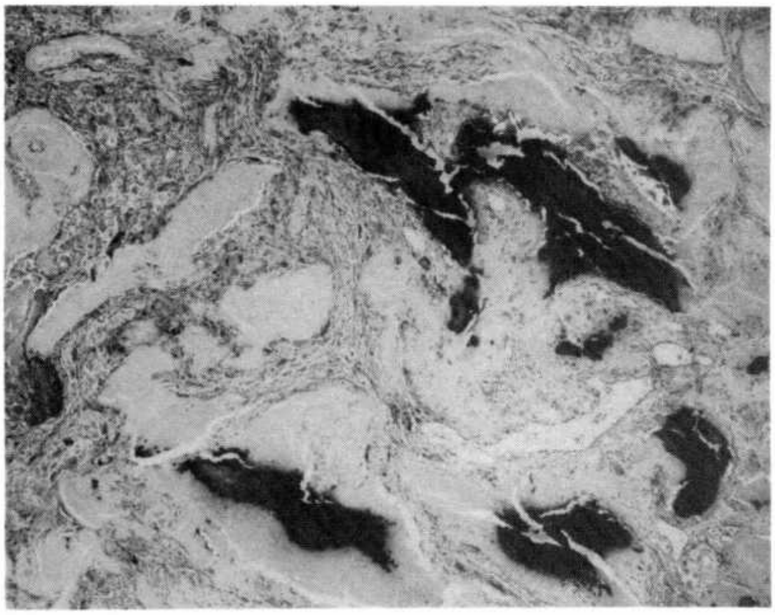


Fig. 6 *Pilomatrixoma. Discernible epithelium is overwhelmed by areas in which the tumour cells have undergone hyaline change and calcification (dark areas). There is a very cellular intervening stroma. (Haematoxylin and eosin, ×36.)*

auricular skin graft (Fig. 9). There has been no recurrence in 18 months.

This case is of particular interest because of the unusually rapid growth rate which was a major cause of clinical confusion. In this respect the tumour is reminiscent of the rare giant pilomatrixomas which have been reported elsewhere,[18] especially in the parotid region,[19-21] but not previously in the context of the eyelids.

Although we have not observed such a case, some authors describe a pilomatrix carcinoma on the basis of frequent mitoses in the basaloid cells and invasion of adjacent fat,[22] muscle, and blood vessels.[23-25] Consequently it has been proposed that all large pilomatrixomas should be excised with wide margins of clearance as in the surgery of BCC.[21] On the other hand large size and rapid growth are not in themselves evidence of malignant behaviour and are not

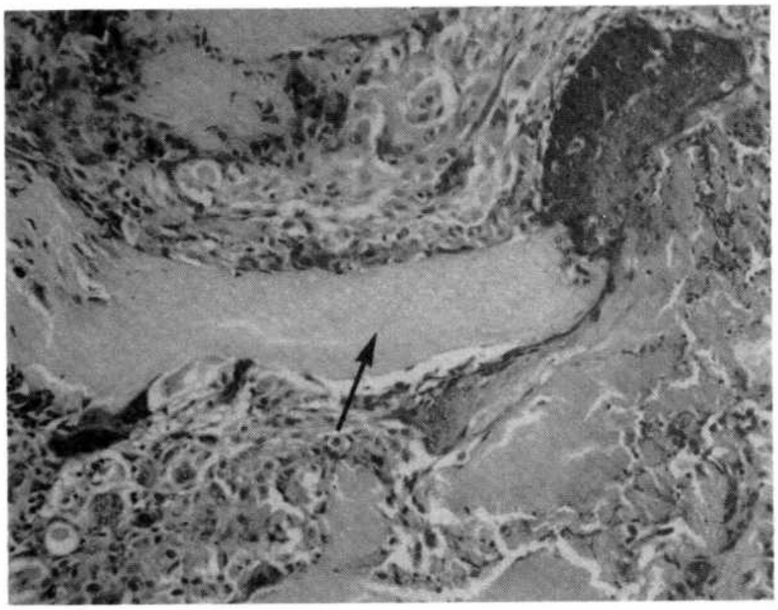


Fig. 7 *Pilomatrixoma. At higher magnification viable epithelium is seen together with areas in which it has been reduced to ghost cell outlines (arrow). The surrounding connective tissue stroma includes several multinucleated giant cells. (Haematoxylin and eosin, ×144.)*

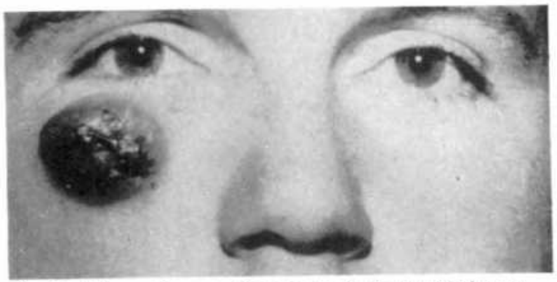


Fig. 8 *Pilomatrixoma. There is a raised, encrusted mass involving the right lower eyelid and adjacent cheek, the nature of which was uncertain prior to biopsy examination.*

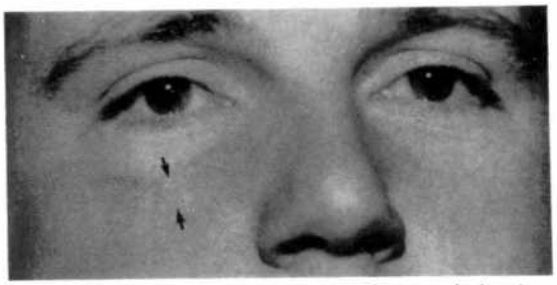


Fig. 9 *Pilomatrixoma. Postoperative photograph showing the resulting defect covered with a whole-thickness postauricular skin graft (between the arrows).*

reliable predictors of the risk of recurrence. Unless evidence of abnormal mitotic cell division and other cytological features of malignancy are revealed in biopsy tissue, there would seem to be little justification for wide excision.

Trichofolliculoma

Histopathology. The essential feature is one or, occasionally, more large cystic spaces containing keratinous material and, frequently, fragments of hair shaft. The cysts are lined by squamous epithelium. Smaller attempts at hair follicle formation are seen radiating from these primary follicles, the fine hairs at the centre of each follicle being surrounded by cells which show peripheral palisading and which are rich in glycogen. The cells forming the inner layer of the hair root often contain eosinophilic trichohyaline granules.

Trichofolliculomas are rare tumours in any part of the skin and are excessively rare on the eyelid. We have observed just one unequivocal case, which involved the upper lid of a 21-year-old male, and know of only three other documented cases concerning the eyelid.[26 27]

Further comments

The object of the present paper is to stress the importance of making a tissue diagnosis in cases of suspected BCC before undertaking definitive surgery, given that occasionally the tumour will prove to be a benign hair follicle lesion which can be safely removed without recourse to wide margins. In which case it is probably useful to summarise the essential clinical and histopathological features of BCC and compare them with the various benign hair follicle tumours:

1. *Incidence.* Over a 30 year period (1958–1987) at the Institute of Ophthalmology we have observed:

Basal cell carcinoma	2447 cases
Trichoepithelioma	18 cases
Trichilemmoma	4 cases
Pilomatrixoma	94 cases
Trichfolliculoma	1 case

2. *Age at presentation.* BCC is uncommon under the age of 50, whereas trichoepitheliomas of the lid can occur at any age, and pilomatrixomas are most frequent before the age of 50. Trichilemmoma also spans a wide age range.

3. *Sex.* There is a predominance of males over females in respect of BCC, trichoepithelioma, and, marginally, trichilemmoma. Sex differences do not appear to be significant with regard to pilomatrixoma or trichofolliculoma.

4. *Clinical appearance and behaviour.* Typically BCC originates as a firm papule which may differ little from the surrounding skin or have a pink translucent appearance. Eventual ulceration leads to the characteristic pearly, rolled edge. Growth is slow and pain is unusual unless there is invasion of bone. However, ulceration is by no means invariable, while conversely, several of the benign hair follicle tumours may occasionally ulcerate and be a source of confusion.

5. *Site.* The lower lid and medial canthus together account for slightly more than three-quarters of BCCs in the eyelid region.[28] Upper lid involvement by BCC is uncommon (less than 7% in one series), whereas it appears to be the predominant site in the case of trichoepithelioma and pilomatrixoma. Trichilemmomas are slightly more frequent on the lower lid.

6. *Histopathology.* The essential feature of BCC is that the proliferation concerns cells which resemble the basal layer of the epidermis or hair follicle in that they have round or oval hyperchromatic nuclei surrounded by a narrow rim of cytoplasm in the absence of the intercellular bridges characteristic of squamous epithelium. A variety of growth patterns is recognised from a solid type that is frequently multicentric, through a reticulate arrangement, to a morphoeic form in which narrow strands of cells run haphazardly within a dense fibrous tissue matrix. It

is this latter variant which is most aggressive and which can be confused with a desmoplastic trichoepithelioma, so that it is important to look for other evidence of hair follicle differentiation to make the distinction. Mucoid degeneration is common in the connective tissue of BCCs, and there may be separation of the affected stroma from the epithelial cell masses due to processing artefact: such separation is said not to occur in desmoplastic trichoepithelioma.

Conclusion

Given the potential for diagnostic error two points of practical importance appear to warrant emphasis. The first is that diagnostic biopsy should be undertaken in respect of all but the smallest tumours suspected of being BCCs prior to definitive excision. The second is that, because confusion can also occur at the histopathological level, the correct diagnosis is more likely to result if surgeon and pathologist share their findings.

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Childhood leukaemia: relapse in the anterior segment of the eye

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SUMMARY A proved first relapse occurred in the anterior segment of eight children with acute leukaemia, two of whom had concurrent central nervous system or bone marrow relapse. A further child developed uveitis after remission was induced, but in this patient no causal relationship with leukaemia was established. Uveitis in children who have had acute leukaemia should be regarded as evidence of relapse, and anterior chamber aspiration and iris biopsy are essential procedures in their evaluation. The outlook for children with anterior segment relapse remains poor despite intensive local and systemic treatment.

The clinical and pathological features of leukaemic infiltration of the anterior segment are well established.[1] Anterior segment changes may be the first manifestation of leukaemia or may reflect the ocular toxicity of antileukaemic therapy[2] The anterior segment is an uncommon site of extramedullary relapse, accounting for between 0·5% and 2·6% of all relapses in large published series[1 3–5] and is seen most frequently in acute lymphoblastic leukaemia (ALL). Two large post-mortem studies of patients with ALL revealed a similar incidence of anterior segment involvement.[6 7] Anterior segment disease is rare in patients with acute non-lymphoblastic leukaemia[8 9] and is very rare in the chronic leukaemias.

The presenting symptoms of anterior segment relapse are generally non-specific, and post-mortem studies show that anterior segment change may occur in asymptomatic eyes.[6] Symptoms include redness, epiphora, and photophobia, and parents may observe changes in the shape and reactions of the pupils or in the colour and appearance of the iris Ocular pain and rarely visual loss also occur.

The clinical findings are very varied, with iritis and hypopyon being the most common. Ciliary injection, fine keratic precipitates with anterior chamber cells, flare,[10–12] posterior synechiae,[11] or a greyish white[14] or bloody[15] hypopyon are found on slit-lamp examination.

Secondary glaucoma with corneal oedema is common.[9] These signs are not pathognomic of leukaemic uveitis, but the diagnosis is suggested by iris thickening, either nodular or diffuse, iris masses, iris colour changes, loss of iris crypts, and rubeosis.[4 8 16 17]

Iris nodules complicated by hyphaema and secondary glaucoma also occur in juvenile xanthogranuloma (JXG). Other causes of spontaneous hyphaema in childhood[13] include retinoblastoma, retrolental fibroplasia, persistent hyperplastic primary vitreous, iridoschisis, unsuspected trauma, iris vascular malformations,[18] rubeosis iridis, and other blood dyscrasias.

There is often uncertainty about the diagnosis that can only be resolved by histological or cytological examination.

Heterochromia and iris discoloration, a JXG-like syndrome,[19] and endophthalmitis[9] have also been the first presentations of leukaemia. In the rare event of leukaemia presenting in the eye[19] it is the failure of response to standard uveitis therapy or progression of the disease with intraocular mass formation which alerts the ophthalmologist to the underlying leukaemia.[9] The diagnosis can be established from histopathological investigations of a peripheral iridectomy specimen[20] or cytological examination of an anterior chamber paracentesis aspirate.[9–11 21 22]

Pathological studies show tumour infiltration of the iris and trabecular meshwork.[6 23] The hypopyon consists of leukaemic cells, necrotic tissue,[9] and proteinaceous exudate.[24] Leukaemic infiltration of or haemorrhage into the iris stroma causes discoloration or heterochromia. Patients with glaucoma have histological evidence of leukaemic obstruction of the outflow channels, including the episcleral vessels,[25]

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but there is no specific pattern of vascular involvement in the anterior segment.[1 23]

Materials and methods

Eleven cases of anterior segment relapse of acute leukaemia in childhood have been referred to the Ophthalmology Department at the Hospital for Sick Children, Great Ormond Street, London, between May 1977 and January 1987. Two had insufficient clinical records to be presented as they were second opinions and not managed or followed up by us.

As part of the routine diagnostic investigations a combined paracentesis and iris biopsy technique is used. We make a partial-thickness 3 mm limbal corneal incision and aspirate some of the aqueous through a 25 gauge needle, which is used to complete the incision. The incision, which is made in the 12 o'clock position of the iris, is increased to full thickness and the iris is induced to prolapse or grasped with forceps. The wound is closed with one buried 10/0 nylon suture and subconjunctival steroids and antibiotics given, followed by topical antibiotics and mydriatics.

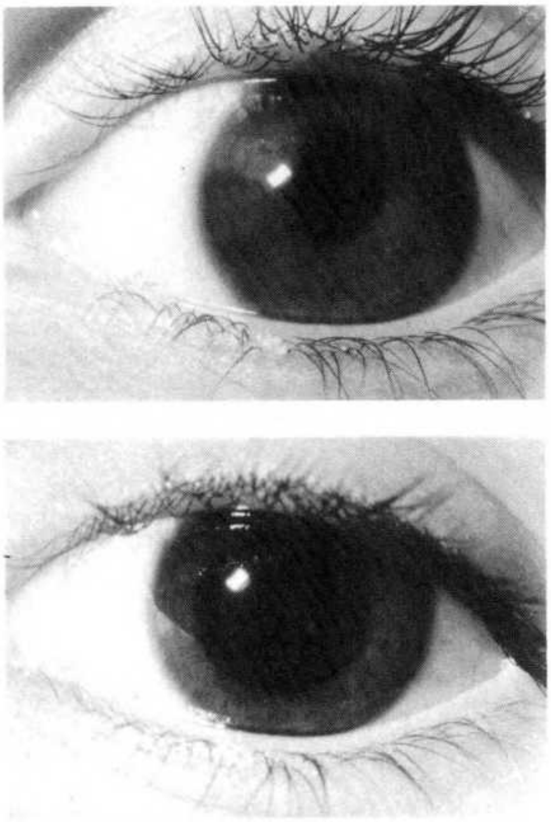

Fig. 1 *Patient 1. Upper figure shows iris thickening, vascularity, discoloration, and pupillary distension. This appearance was also seen in patients 2, 3, 5, and 7.*

Case reports

We present the clinical and pathological data on patients whose first haematological remission was terminated by a recurrence of leukaemia in the anterior segment or was complicated by uveitis.

CASE 1

A boy of 3 years 4 months was found to have ALL without evidence of central nervous system (CNS) involvement. Remission was successfully induced and maintained on the UKALL V regimen.[26] All treatment was discontinued after 26 months. Four months later he presented with sudden onset of pain in his right eye. On examination iritis with hypopyon and a diffusely thickened iris were seen (Fig. 1). Anterior chamber paracentesis and iris biopsy confirmed infiltration by leukaemic lymphoblasts. Local radiotherapy resulted in his anterior chamber appearances returning to normal.

CASE 2

A girl of 2 years 1 month presented with recurrent infections, pallor and fever. Laboratory data included a leucocyte count of $22{\cdot}0\times10^9/l$ with 31% lymphoblasts. Bone marrow examination confirmed the diagnosis of ALL. Examination of the cerebrospinal fluid (CFS) was normal. Remission was induced with a modified UKALL IV regimen,[27] and continuation therapy was stopped 31 months after diagnosis. Relapse in the anterior chamber (AC) was diagnosed one month later during investigation of recurrent unilateral left conjunctivitis. On examination a solid white mass in the anterior chamber was noted together with multiple deposits throughout the iris. A diagnosis of ALL infiltration was made by an anterior chamber paracentesis. Local radiotherapy resulted in a rapid improvement apart from the appearance of a small lens opacity.

CASE 3

This patient first presented at age 3 years with fever and malaise. Laboratory findings included leucocytes $30{\cdot}2\times10^9/l$ with 80% blasts. Bone marrow examination confirmed the diagnosis of ALL. She had no evidence of CNS involvement. She was treated with vincristine, prednisolone, asparaginase, and daunorubicin induction, craniocervical irradiation (1800 cGy) and intermittent vincristine, prednisolone methotrexate and 6-mercaptopurine continuation chemotherapy for a total of 26 months. One month later she was noted to have anisosocoria.

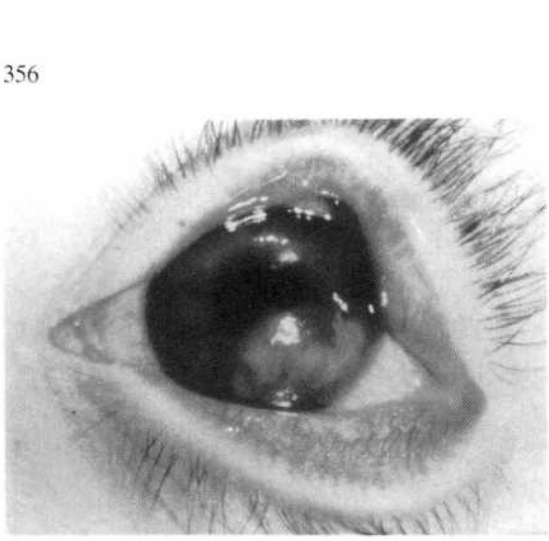

Fig. 2 *Patient 4. This child had an ocular relapse with a solid mass. Patient 8 had a similar appearance.*

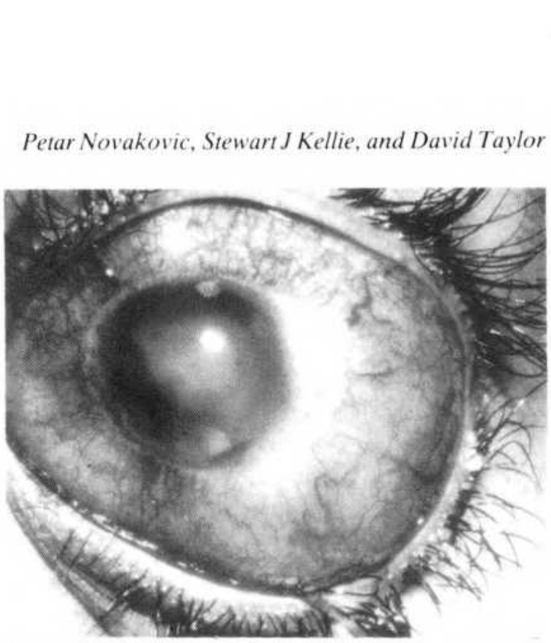

Fig. 3 *Patient 6 had an ocular relapse treated initially with topical and systemic steroids, later with 150 cGy. This appearance, with the eye destroyed by recurrent tumour was seen five months later.*

Examination revealed a few cells in the left anterior chamber and some iris irregularities. Anterior chamber paracentesis revealed the cause of the iritis to be recurrent ALL. She was given a total of 2300 cGy radiotherapy to her left eye, with complete resolution of her ocular signs. Five months later she was diagnosed as having moderately severe bilateral iritis, again assumed to be due to ALL.

Anterior chamber paracentesis did not reveal the cause of the iritis, which responded well to topical steroids and mydriatics. A further five months later she suffered another episode of bilateral iritis. She was given a total of 2500 cGy radiation to each eye, with good resolution. She is developing a small left lens opacity but remains free of recurrent leukaemia.

CASE 4

This patient presented at age 10 months with a leucocyte count of $3{\cdot}0\times10^9$/l with 12% lymphoblasts. Bone marrow examination revealed ALL. There was no evidence of CNS involvement. She received similar treatment to patient 3, although craniocervical irradiation (1500 cGy) was deferred until after age 2 years. Treatment was continued for 25 months. Her presentation with a red left eye coincided with the elective discontinuation of therapy. Examination showed an oedematous cornea, raised intraocular pressure, and iris infiltration with a solid mass (Fig. 2). Anterior chamber paracentesis revealed blast cells. Radiotherapy of 2500 cGy resulted in a return to a near normal anterior segment, apart from a slightly peaked pupil due to peripheral anterior synechiae superiorly.

CASE 5

This 3½-year-old boy was found to have ALL following presentation with fever and knee pain, and leucocyte count of $2{\cdot}4\times10^9$/l with 9% blasts. No blast cells were seen on CSF cytospin. He was treated on the UKALL X regimen.[28] He first developed features of a left sided unilateral conjunctivitis 17 months after diagnosis of ALL.

His symptoms fluctuated during the following month, and when he was first seen on our department he had cells in the anterior chamber. His symptoms continued to fluctuate over the subsequent two months. An anterior chamber paracentesis and iris biopsy were performed, revealing blast cells. At the time of anterior chamber paracentesis, during the second year of continuation chemotherapy, he was found to have a bone marrow relapse.

CASE 6

A boy from the Middle East with ALL was referred one year after diagnosis with photophobia and pain in his left eye radiating to the temporal region. On examination conjunctival congestion, haziness of the cornea, slight proptosis, and evidence of panuveitis were noted. He was treated with topical and systemic steroids without improvement. A single fraction of 150 cGy was given at his local hospital because of deteriorating vision. He was referred five months later. The internal structures of his left eye was destroyed by tumour (Fig. 3), and further investigation disclosed evidence of CNS relapse. A CT scan demonstrated infiltration of the whole eye and optic nerve. He was treated with palliative radiotherapy to his lefe eye. However, he experienced bone marrow and CNS and bilateral ocular relapses and died.

CASE 7

This boy was diagnosed as having ALL at the age of 9 months. Remission was induced with vincristine, prednisolone, and L-asparaginase. He received triple intrathecal chemotherapy but no cranial irradiation because of his young age. At the age of 2 years and 1 month he presented with an acutely inflamed right eye, which proved to be due to leukaemic infiltration on anterior chamber paracentesis and iris biopsy. He received further induction chemotherapy, cranial and local radiotherapy, and has remained disease free.

CASE 8

At 5 months this child presented with acute monocytic leukaemia. Remission was induced with intensive chemotherapy, complicated by septicaemia and was associated with bacterial colonisation of her central venous line. At 9 months of age, during her third course of chemotherapy, she developed a red left eye with uveitis. An iris biopsy and anterior chamber paracentesis confirmed the presence of leukaemic blasts. Local ocular radiotherapy was begun but was complicated by iris prolapse, which was repaired, however. She died aged 10 months of septicaemia from Gram-negative organisms.

CASE 9

This 5-year-old boy had been seen by an ophthalmologist at age 3 years for a pseudo squint, with no abnormality detected. He developed ALL in May 1984, and treatment was stopped electively in July 1986. His mother sought the advice of an ophthalmologist because he failed a school eye test. The only significant abnormality found on examination was cells in both anterior chambers and a fine keratic precipitate. An iris biopsy and AC paracentesis revealed inflammatory cells. He was treated with subconjunctival depot steroids and has been free of symptoms and abnormal signs for nine months.

Discussion

The mechanism of anterior segment relapse is not clear. Migration of leukaemia lymphoblasts along the posterior ciliary vessels in the subarachnoid space surrounding the optic nerve had been proposed as a mechanism linking the central nervous system and the anterior segment.[10] Although the pathogenesis of anterior segment disease is unknown, the infrequency of concurrent CNS relapse and anterior segment relapse suggests that seeding from the CNS is unlikely to be an important mechanism. The frequency of isolated anterior segment relapse supports the sanctuary concept of the anterior chamber.[11] Care is taken to exclude the anterior chamber from 'prophylactic' central nervous system irradiation.

Extensive ocular leukaemic infiltration is exceptionally rare and easily recognised, but the diagnosis in children with intermittent iritis, as in case 5, or refractory iritis, as in case 3, is less obvious. Examination of an anterior chamber aspirate has been the most widely used technique for establishing a diagnosis, but we would not support this as a sole means of obtaining an accurate diagnosis because of the difficulty in interpreting the significance of the few abnormal cells on cytospin of fluid obtained by aspiration. Cytochemistry, surface immunological markers, cytogenetics, or possibly molecular studies might change this, but at the moment we use a combination of iris biopsy and paracentesis. The technique of aspiration or paracentesis is important because the child may be debilitated and immunosuppressed, and healing may be further delayed by radiotherapy. In addition the intraocular pressure is likely to be severely raised from time to time by crying.

Six of our cases had iris biopsy, which revealed the exact cause of the iritis, enabling more accurate characterisation of the infiltrating cells. Iris biopsy has a very low surgical complication rate and is indicated in the leukaemic child with iritis, when there is even the least doubt about the diagnosis. In case 7, for instance, the clinical certainty was so high, and the therapeutic alternatives so few, that neither biopsy nor aspiration were indicated. In contrast, in patient 9 the result was that no leukaemic cells were found and the uveitis responded to topical steroid treatment only, with no recurrence of leukaemia over nine months. In case 3, although there was some difficulty with the interpretation of the second iris biopsy and AC aspirate, radiotherapy and reinduction chemotherapy brought about a prolonged period of freedom from uveitis.

That the uveitis is not necessarily related to leukaemic ocular relapse, as in case 9, emphasises the need for accurate diagnosis. In view of the rarity of childhood uveitis it is also puzzling that a non-leukaemic uveitis should occur so closely related to the cessation of chemotherapy. Perhaps in this instance the uveitis was not related to the leukaemia so much as the treatment, or the associated immunosuppression, as occurs in patients receiving bone marrow transplants.

We have had one significant complication of iris biopsy: in patient 8 an iris prolapse occurred one week after biopsy during radiotherapy. It was closed without recurrence. We considered it was due to a combination of raised intraocular pressure from iritis and crying and a wound whose healing was compromised by chemotherapy and radiotherapy.

Table 1 *Clinical details of children with anterior segment relapse*

Patient	*ASR on/off CT*	*Concurrent relapse*	*Duration of first remission† (months)*	*Further therapy*		*Duration of second remission (months)*	*Subsequent relapse (site)*	*Survival at Nov 1987 following initial ASR (months)*
				Eye	*Systemic*			
1	Off	—	29	2400 cGy	UKALL V[25]	33	BM	76
2	Off	—	31	2400 cGy	UKALL V[25]	13	BM	14
3	Off	—	26	2300 cGy	UKALL X[27]	41+	—	45+
4	On	—	24	2500 cGy	Repeat initial therapy	18	BM	21
5	On	BM	16	1200 cGy	UKALL X[27] CPA TBI, ABMR	1	BM	6
6	On	CNS	10	2550 cGy	VCR 6MP MTX	. 2	BM, CNS, Bilateral ASR	12
7	On	—	13	2400 cGy	VCR Pred, Asp	12+	—	15+
8	On	—	4	2400 cGy	MAZE	—	—	1*

CT=continuation chemotherapy BM=bone marrow. CNS=central nervous system VCR=vincristine. 6MP=6 mercaptopurine. *Died from Gram-negative septicaemia. MTX=intrathecal methotrexate. RT=craniocervical radiotherapy. Pred=prednisolone MAZE=M-AMSA, 5 azacytidine, etoposide CPA=cyclophosphamide TBI=total body irradiation ABMR=autologous bone marrow rescue. Asp=asparaginase. †First remission terminated by AC relapse ASR=anterior segment relapse

Tumour regression and lowering of intraocular pressure have been the aims of ocular therapy. Topical steroids and periocular steroid injections have had variable success in reducing the severity of the iritis or arresting tumour infiltration. Irradiation yields more reliable results and is effective in most forms of anterior segment leukaemia both in inducing clinical tumour regression and in controlling the secondary glaucoma.[17] Initial doses administered have varied from 250 to 1500 cGy [22] Case 7 had 250 cGy and this was followed by progression within the eye and around the optic nerve sheath and ultimately into the suprasellar cistern, from which death resulted despite treatment. The poor prognosis in our patients may be a reflection of the significance of sanctuary site relapse and emphasises the need for optimal local treatment. Despite our relatively high total doses of 2300 to 2500 cGy (Table 1), followed by complete clinical regression, long-term systemic prognosis is still poor and in two cases was followed by further ocular relapse. The ocular prognosis depends on the nature of the eye relapse: if there has been a solid recurrence there is usually structural eye damage, which may be irretrievable. All but one patient (6) retained useful vision in the involved eye.

When the biopsy and aspirate do not show leukaemic infiltration, it is important to consider the prior treatment that the child has received. Steroids may mask the real cause of the uveitis, and their preoperative use should be avoided.

Enucleation of an eye that is the site of recurrent isolated anterior segment relapse is rarely indicated. Jankovic *et al.*[23] reported an adolescent in prolonged second remission following enucleation. High-dose systemic chemotherapy has induced temporary remissions of anterior segment relapse.[29] However, this therapy alone appears to be ineffective in ensuring prolonged disease-free survival.

Patients with prolonged second remissions received intensive combination systemic chemotherapy, prolonged continuation therapy, and local irradiation. The prognosis for children with anterior segment relapse remains poor despite aggressive local and systemic treatment because of a substantial risk of subsequent bone marrow or CNS relapse. The timing of AC relapse is important in predicting which patients are at greatest risk of dying of recurrent leukaemia.[9,30,31]

We believe the goal of therapy in any child with AC relapse is cure and that every patient with uveitis within six years of achieving first remission in ALL should undergo iris biopsy and cytospin examination of AC aspirate followed by intensive retreatment.

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Relative bioavailability of pilocarpine from a novel ophthalmic delivery system and conventional eyedrop formulations

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SUMMARY Pupillary responses to pilocarpine following topical application in a novel ophthalmic delivery system (NODS) and a conventional eyedrop formulation have been compared in eight healthy subjects in a single dose crossover study. The magnitude of the miotic and light reflex responses to NODS 40, 80, and 170 μg and to a single 2% Minims eyedrop (delivering 518 μg) were recorded by infrared television pupillography over periods of 24 hours. Dosage comparisons of drug responses were obtained by interpolation and yielded the equivalence of one eyedrop to 67±11 μg pilocarpine from the NODS formulation. These findings indicate that in a comparison of total doses delivered pilocarpine has an approximately eight-fold greater bioavailability from NODS than from a conventional eyedrop formulation.

Pilocarpine is conventionally applied as eyedrops in aqueous solutions of various concentrations. Alternative technologies for drug delivery have been developed (solutions in castor oil, Ocuserts, and others), but these have not found wide clinical application. A novel ophthalmic delivery system (NODS) has recently been designed to deliver a precise amount of the drug to the eye. The medication is incorporated into a water-soluble polyvinyl alcohol (PVA) film which detaches from the rest of the device (a stiffened paper strip handle) when placed in the lower conjunctival sac (Fig 1). The medicated film (length 4 mm, width 6·3 mm, thickness 20 μm, volume 0·5 μl) dissolves in the tear fluid releasing the medication. The overall length is 55 mm, the whole device being of similar size to a Fluoret. The NODS contains no preservative and is sterilised by gamma radiation.

We report here a study in healthy volunteers designed to compare bioavailabilities from NODS and conventional eyedrop formulations.

Material and methods

Subjects. Eight healthy subjects (4 M, 4 F) aged 19 to 36 years took part in the study. None had a previous history of cardiovascular, respiratory, or eye disease, and all had normal eyes, intraocular pressure (IOP), blood pressure, electrocardiogram (ECG), and haematological and biochemical profiles. One female subject was taking oral minocycline 50 mg daily; there were no other drug treatments. Each gave written consent to participate, and the study was approved by the Ethics Committee of West Lambeth Health Authority.

Treatments and study design. Subjects attended on four occasions at the same time of day separated by at least seven days No caffeinated drinks or smoking were permitted on experimental days. On each occasion one of four treatments, each containing pilocarpine nitrate, was administered in a single dose to one eye only in a complete balanced crossover design using two Latin squares. The four treatments were: NODS 40 μg, NODS 80 μg, NODS 170 μg,

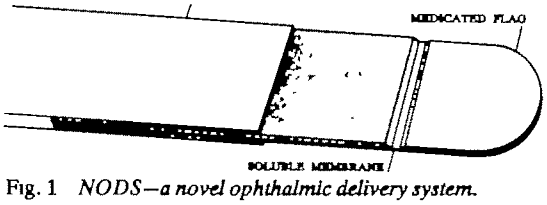

Fig. 1 *NODS—a novel ophthalmic delivery system.*

Correspondence to Professor S E Smith, Department of Clinical Pharmacology, St Thomas's Hospital, London SE1 7EH and 2% aqueous eyedrops (a single drop delivered from Minims pilocarpine 2%). The average weight of an eyedrop was independently recorded and calculated to deliver 518 μg of pilocarpine nitrate.

Measurements. Before and at 15, 30, 45, 60, 75, and 90 min, and at 2, 3, 4, 6, 9, and 24 h after treatment, darkness pupil diameters and amplitudes of reflex responses to 0·5 s light flashes were recorded from both eyes by infrared television pupillography as previously described.[1] Drug effects on diameter and light reflex amplitude at each time were calculated as differences between treated and untreated eye. The total miotic response was calculated as the area under the curve from time 0 to 24 h by the trapezoid rule. Effects on the light reflex were calculated as percentage inhibition.

The subjects were questioned about local adverse effects of the formulations, stinging, foreign body sensation, and eye watering at 1 and 20 min after treatment and the results graded 0 (absent), 1 (mild), 2 (moderate), or 3 (severe).

Statistical analysis. The repeatability of the measurements of pupil diameter and light reflex amplitude was assessed from the pretreatment data by analysis of variance. The values, which were derived from the within-subject residual mean square, yielded coefficients of variation as follows: pupil diameter, 3·6%; light reflex amplitude 11·1%. The intraocular differences showed poor repeatability because of the low mean differences involved, but the standard deviations were in each case small by comparison with the changes induced by drug treatment.

In each subject graphs of the log dose pilocarpine-response relationships for the NODS formulations were plotted and the equivalent dose for the eyedrop formulation calculated by interpolation. Mean values, standard errors of mean, and 95% confidence intervals for these estimates were calculated by standard methods.

Results

Pilocarpine constricted the pupil in all doses studied. The time course of this constriction is shown in Fig. 2. Peak responses occurred at median times of 0·75 h (NODS 40 μg and 80 μg) and 0·5 h (NODS 170 μg and eyedrops) without significant difference between them. The magnitude of the peak effects were ranked in order: NODS 170 μg>NODS 80 μg>eyedrops >NODS 40 μg. Light reflexes were inhibited in parallel with miosis. Mean peak effects and area under the curve (AUC) are given in Table 1.

The dose-response relationship for pupillary constriction from NODS formulations was non-linear, the highest dose used (170 μg) producing an effect close or equal to a maximum (Fig. 3). The dose of the eyedrop formulation was submaximal in its effect, and the calculated NODS equivalence was 67·1 (SEM 10·7) μg with 95% confidence intervals of 45·7 and 88·5 μg (Table 1). The relationships for the total miosis (AUC) and for light reflex inhibition yielded almost identical figures. On the basis that one eyedrop delivered 518 μg pilocarpine, these findings indicate in terms of total dosage an increase in relative bioavailability of the NODS formulation of 518/67·1 or 7·7-fold.

No serious side effects or adverse reactions were experienced. A number of subjects complained of local effects immediately following instillation of the NODS or eyedrops. Application of NODS induced a transient foreign body sensation in the eye on 22 of 24 occasions but eyedrops did so on only 1 of 8 occasions

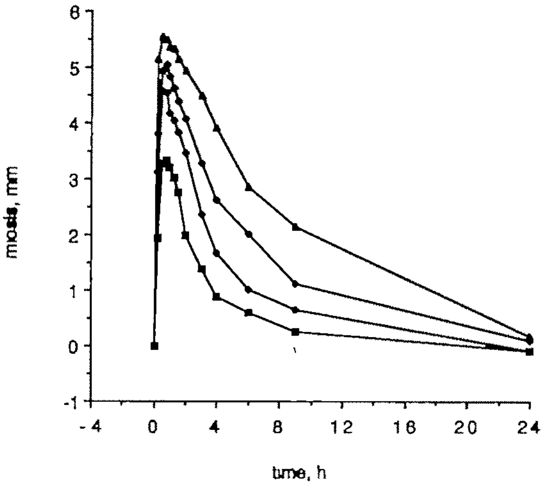

Fig. 2 *Mean pupillary constriction responses to pilocarpine following application of NODS 40 μg (■——■), 80 μg (◆——◆), and 170 μg (▲——▲) and eyedrop formulations (◇——◇)*

Table 1 *Pilocarpine-induced peak miosis, total response (area under the curve—AUC), and light reflex inhibition following administration as NODS and eyedrop formulations Values expressed as mean (SEM)*

	Peak miosis (mm)	*AUC Miosis (mm h)*	*Light reflex inhibition (%)*
NODS 40 μg	3·42 (0·58)	12·23 (2·78)	60·3 (8·8)
NODS 80 μg	5·07 (0·36)	33·78 (7·04)	88·2 (5·0)
NODS 170 μg	5·67 (0·38)	50·70 (7·34)	95·0 (1·7)
Eyedrops 2%	4·65 (0·47)	22·07 (4·78)	78·4 (4·1)
NODS equivalent of eyedrops (μg)	67·1 (10·7)	65·6 (10·8)	68·5 (18·3)
(95% Confidence interval)	45·7–88·5	45·1–87·2	31·9–105·1

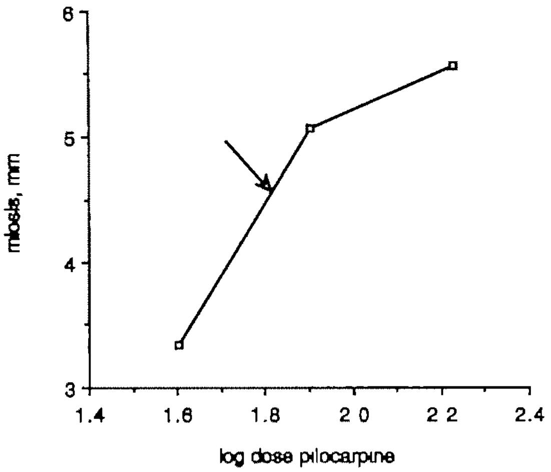

Fig 3 *Log dose/mean peak response relationships for pilocarpine following application of NODS (40, 80, and 170 μg). The arrow indicates the mean peak response for the eyedrop formulation.*

($\chi^2=19{\cdot}014$, $p<0{\cdot}001$). In only one subject on one occasion did mild discomfort persist for 20 min Stinging and eye watering occurred equally with the two types of formulation.

Intense miosis in response to the treatments was associated with eye or brow ache on the treated side during the first two hours after instillation. Headache, severe enough to require medication with paracetamol, occurred in two subjects thereafter. These responses were dose related and not associated with a particular formulation.

Discussion

The quantity of drug applied to the eye from conventional eyedrops is necessarily high because of the low bioavailability from this route. At least 80% of the volume of an administered eyedrop drains rapidly through the nasolacrimal duct, allowing for subsequent systemic absorption.[2] The use of polyvinyl alcohol as a vehicle for ophthalmic drugs, first described in Russia in 1964,[3] greatly improves bioavailability.[1] The results of the present study indicate that pilocarpine in NODS can be applied at 8 times smaller dosage than in eyedrops with a proportionally reduced risk to the patient of systemic side effects. Clinically pilocarpine eyedrops rarely produce such effects when used in chronic simple glaucoma, but the high dose and frequency of treatment in acute glaucoma may cause the classical signs of muscarinic receptor overstimulation. The resulting symptoms include increased salivation, nausea, vomiting, diarrhoea, bronchospasm, and pulmonary oedema.[4 5]

Many different ophthalmic drugs could be delivered in NODS vehicles. The serious systemic side effects from beta-blocker therapy in chronic simple glaucoma in particular might thereby be reduced.

The volunteers in this study tolerated NODS reasonably well and the ease of application was comparable to eyedrops. The transient foreign body sensation might discourage some patients. Polyvinyl alcohol is thought to be non-irritant to the eye,[6] and the small film in NODS has not been associated with adverse reactions in other studies.

We thank Smith and Nephew Pharmaceuticals for a gift of the materials and for financial support. SAS is supported by the Research Endowment Committee, Special Trustees of West Lambeth Health District.

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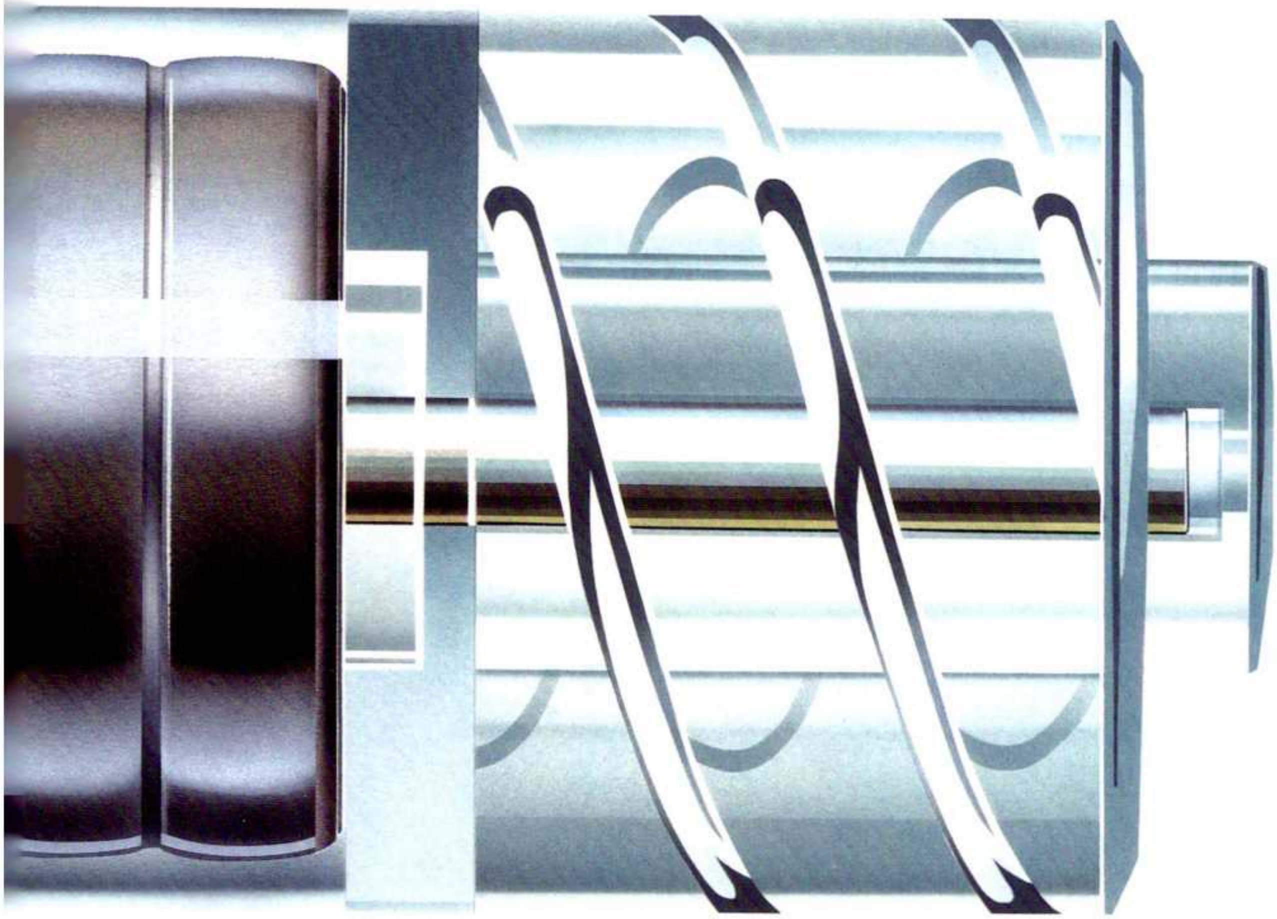

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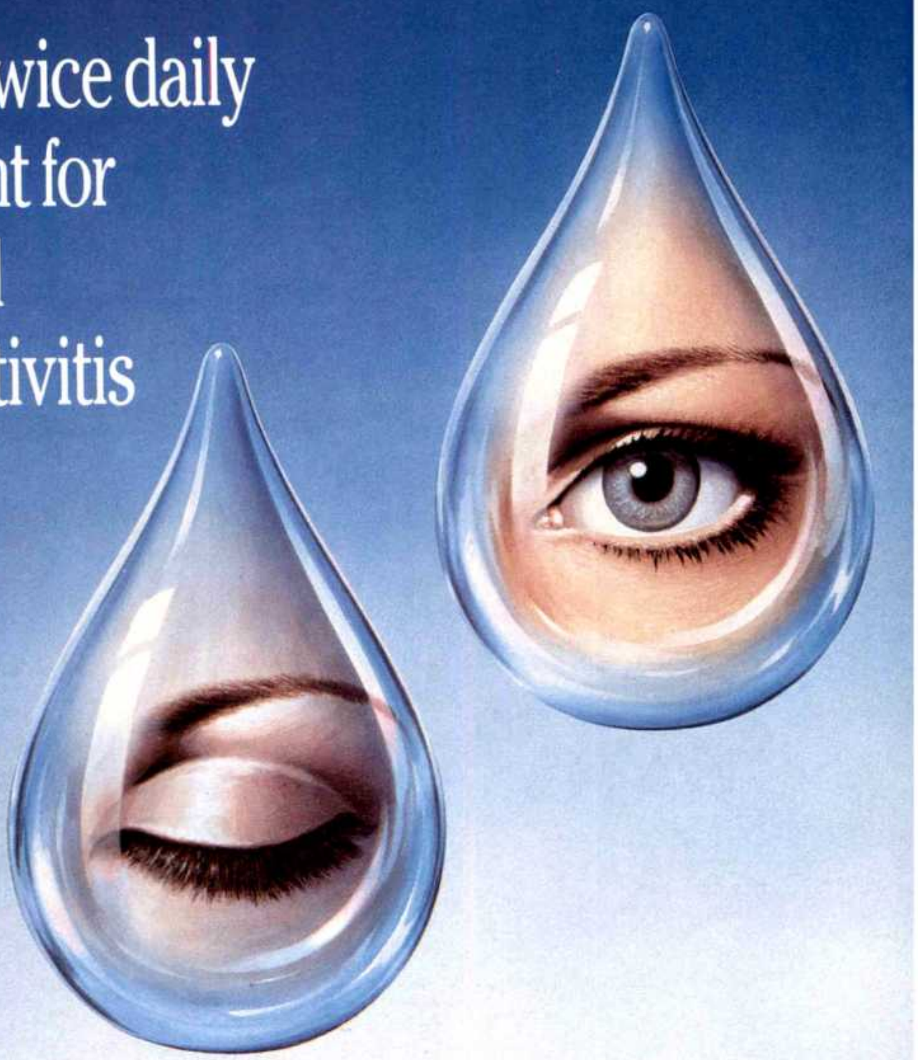

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British Journal of Ophthalmology, 1989, **73**, 363–364

Spontaneous intracorneal haemorrhage

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SUMMARY We describe the unusual complication of spontaneous intracorneal haemorrhage in a patient who used an extended-wear contact lens. This was severe enough to cause corneal blood staining and ulceration which required surgical intervention.

A 65-year-old male Caucasian bricklayer who was otherwise fit and who had had no previous eye disease underwent an uneventful intracapsular cataract extraction through a standard limbal incision to the left eye in October 1979 and to the right eye in February 1981. He was subsequently fitted with 30% Hydrogel daily wear contact lenses in June 1981 and achieved visual acuities of 6/9 (left) and 6/6 (right). Unfortunately he often failed to attend for treatment and also misused these lenses by wearing them on an extended-wear basis. This, together with lens spoilation due to lipid deposition, became a problem, and he was subsequently fitted with 60% Hydrogel lenses in March 1982 for use on an extended-wear basis.

He presented in April 1982 complaining of painful blurring of vision in the right eye for three days. His vision had dropped from 6/6 to counting fingers, and he was found to have a central superficial corneal ulcer with a little stromal ulceration associated with a brisk anterior uveitis but no hypopyon. A frond of deep corneal vessels at the level of Descemet's membrane was noted at 9 o'clock, away from the previous limbal section and extending half way to the visual axis. He was admitted to hospital with a diagnosis of suppurative keratitis. Microbiological investigation, including superficial corneal scraping, revealed no organisms, but he was treated with an atraumatic subconjunctival injection of 20 mg gentamicin and Mydricaine no. 2 (atropine sulphate, procaine, adrenaline solution) followed by intensive topical antibiotics and mydriatics.

The following day the eye was more comfortable and clinically much quieter, but he had developed a small intracorneal haemorrhage in the posterior third of the corneal stroma arising at the temporal limbus and extending 2 mm towards the visual axis. Over the next few hours this gradually enlarged, with an obvious horizontal blood level, but this progression halted when approximately 4 mm from the limbus, leaving the visual axis unaffected. Two days later the ulcer, uveitis, and infiltration had almost cleared, but he then developed a further secondary intrastromal haemorrhage which obscured the visual axis reducing the vision to hand movements only.

Investigations revealed a normal blood profile and no bleeding disorder. At no time during this episode did he have blood in the anterior chamber, any increase in intraocular pressure, or any significant stromal oedema.

Over the next few months the eye remained quiet, with a visual acuity of hand movements only, but the corneal stroma developed diffuse central and inferotemporal blood staining. In July 1982 he developed pain and watering in the right eye and was found to have an area of central corneal stromal breakdown and very deep ulceration over the blood stained area (Fig. 1). The iron-derived pigment in the ulcer base

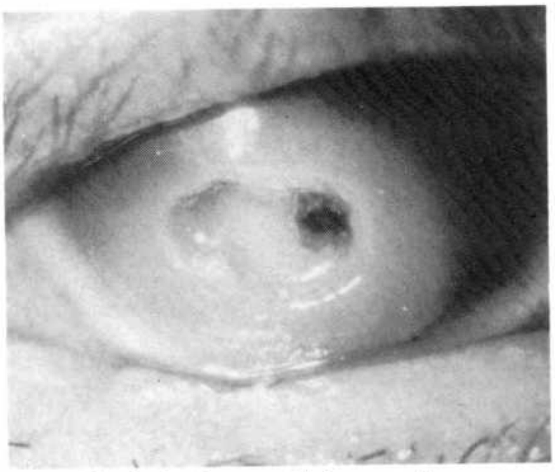

Fig. 1 *Blood stained cornea with deep central corneal ulcer, a part of which is pigmented.*

Correspondence to Mr M G Falcon, FRCS.

looked suspiciously like iris, but there was no leak, the anterior chamber was deep, and the pupil was round.

He was treated with chloramphenicol drops four times a day, but the ulcer enlarged and deepened. A bandage contact lens was not tolerated. Because the corneal pathology was purely stromal and there had been no suggestion of endothelial compromise, and because the disease had by now extended to the limbus, an 8 mm diameter, deep lamellar keratoplasty was carried out in September 1982. At operation he was found to have a large pool of gelatinous altered blood between the stroma and Descemet's membrane. This was removed together with the blood stained cornea, and a pre-Descemet's lamellar graft was carried out. A small amount of residual blood remained. Postoperatively he achieved a visual acuity of 6/9 with a gas permeable daily-wear contact lens. Good vision with the contact lens has continued to date.

Endothelial specular photographs taken a month after grafting showed enlarged but plentiful endothelial cells centrally with some variation in size. This was felt to be consistent with an otherwise uneventful cataract extraction and supported the choice of lamellar keratoplasty rather than penetrating keratoplasty in this case.

Discussion

This patient had two unusual corneal problems: (1) spontaneous intracorneal haemorrhage; (2) corneal blood staining without endothelial involvement leading to ulceration and requiring lamellar keratoplasty.

The intracorneal haemorrhage arose from deep stromal vascularisation, which was the result either of using the extended-wear soft contact lens or suppurative keratitis. The short history of the latter makes this an unlikely cause. Extended-wear soft contact lenses can lead to deep stromal vascularisation, but superficial corneal vascularisation is commoner.[1] It has also been reported in patients using cosmetic, daily-wear soft and hard lenses.[2]

Intracorneal haemorrhage is an uncommon event. The reports show that a third of them have occurred after intraocular surgery such as cataract extraction or corneal grafting; another third followed ocular trauma; and the final third were associated with inflammatory corneal disease such as corneal ulcers and chemical burns.[3]

Only two cases of spontaneous intracorneal haemorrhage secondary to vascularisation induced by a contact lens have been reported.[4,5] Both followed the use of daily-wear soft contact lenses in aphakic eyes and both were subepithelial haemorrhages. The first cleared spontaneously in three weeks, the second was extensive and required debridement. The haemorrhage in our patient occurred at a much deeper level and was severe enough to cause extensive stromal blood staining and subsequent necrosis and ulceration of a large area of stroma, which required lamellar keratoplasty. Recently Ormerod and Egan[6] described three cases of intracorneal haemorrhage secondary to microbial keratitis, two of which were subepithelial and cleared rapidly. The other was mid-stromal and pre-Descemet's and was still present after one month.

Corneal blood staining classically follows traumatic hyphaemas where there has been severely raised intraocular pressure and compromised endothelial function.[7] But cases have been reported of staining occurring in patients with traumatic hyphaemas and low intraocular pressures[8] The mechanism postulated in these cases was that the staining was secondary to contusion necrosis of the endothelium or to temporary endothelial decompensation in the presence of significant hyphaemas. Corneal blood staining in our case occurred as a direct result of haemorrhage within the cornea Corneal blood staining generally clears spontaneously, though it may take up to three years.[8] For reasons that are not clear this patient developed stromal necrosis and ulceration.

We are grateful to Mr B Cobb, FRCS, consultant ophthalmologist, Greenwich District Hospital, for referring the patient and allowing us to publish this report.

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A pilot project of glaucoma in Barbados

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SUMMARY The prevalence of open-angle glaucoma is believed to be very high among West Indian blacks. To begin investigating the prevalence and risk factors for glaucoma and other eye diseases in Barbados, WI, a pilot study was conducted. The pilot project identified a stratified, random national sample of 300 persons over 35 years of age who were invited to participate in an ophthalmic examination and an interview. Of those contacted 89% were eligible and 95% of these agreed to participate. The overall glaucoma prevalence in the participants was 6%; it was 13% among black and mixed persons over 54 years. Age related cataract, hypertension, and diabetes were frequent findings. Although the sample size of the pilot project is small, the results suggest a high prevalence of glaucoma in Barbados, a finding that merits further study.

Open-angle glaucoma is a major cause of visual impairment in black populations.[1-4] While the prevalence of glaucoma in whites is relatively low—around 1% or less at ages under 70 years,[5-9] several studies suggest a much higher frequency in populations of African descent.[2-4] Among US blacks the incidence and prevalence of blindness registration from glaucoma is eight times higher than in whites.[1] A large difference in rates is reported for all sexes and all age groups, with a non-white/white ratio of 15:1 at ages 45–64 years. In addition these data show a younger age at blindness registration for blacks than whites and a more advanced stage of visual impairment, suggesting an earlier age at onset and a more severe course of disease. As reviewed elsewhere,[10 11] the available epidemiological data on risk factors are extremely limited, and the reasons for the high susceptibility of black populations to glaucoma remain unknown.

An unusually high glaucoma risk among West Indian blacks has been reported.[4 12 13] In Barbados, WI, the disease is considered to be the major cause of blindness, presenting with advanced optic nerve damage at an early age[12 13] (and personal communication from the ophthalmologists in Barbados). Medical treatment has limited effectiveness at this stage of the disease. To study adequately the glaucoma problem in Barbados epidemiological data are needed on the prevalence and risk factors for the disease in this population.

An additional obstacle to the development of effective programmes to prevent or control visual loss is that very little is known about the epidemiology of other eye diseases in black populations. Few studies have determined prevalence and risk factors for age related cataract, macular degeneration, or diabetic retinopathy in such populations. Clinical studies in Africa found a low frequency of maculopathy,[14 15] but a somewhat higher prevalence has been reported for US blacks than whites.[16] High prevalences of diabetic retinopathy[17-19] and of diabetic retinopathy blindness in blacks have been reported[20] as well as a higher cataract prevalence in US blacks than whites.[16] Data on risk factors, however, are very limited.

As a first step toward obtaining epidemiological data on the prevalence and risk factors for glaucoma and other eye diseases in a black population a pilot project was undertaken. The pilot project was designed to assess the extent of population participation in such a study as well as to test the proposed data collection methods. This paper reports the findings of that pilot investigation.

Material and methods

The island of Barbados, which has over 250 000 inhabitants in an area 21 miles long and 14 miles wide (34 by 23 km), is one of the countries with the highest population density.[21 22] As described elsewhere,[23] the pilot study was based on a stratified random sample of the adult population of Barbados; the sample was

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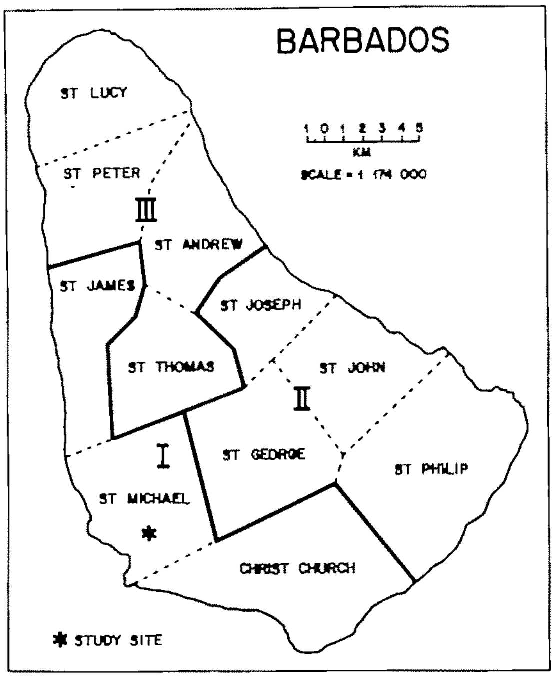

Fig. 1 *Map of Barbados showing geographic regions in the sample*

drawn by randomly selecting 100 persons aged 35 years and over from each of three geographic strata. Stratum I included the highly urban regions of the country, with densities of 550–2500 persons per km^2; stratum II was an intermediate region with densities of 300–400 persons per km^2; and stratum III included the less populated regions with densities of under 300 persons per km^2 (Fig. 1). The sample was drawn from the Barbados National Register by the Barbados Statistical Service.

An invitation to participate in an eye examination at a Ministry of Health polyclinic was mailed to individuals included in the sample; telephone calls and/or home visits were made to schedule appointments. In the polyclinic all study participants had anthropometric and blood pressure measurements done, glycosuria screening, refraction and visual acuity testing with a Humphrey Automated Refractor 530, perimetry with a Humphrey Visual Field Analyzer 620, applantation tonometry, an interview to ascertain risk factors, fundus photography, and an examination by an ophthalmologist.

Screening for visual field defects used the 120-point 3-zone scheme of the Humphrey Analyzer. Whenever a screening field had 17 or more absolute or relative defects or eight or more defects clustered in one area, participants were retested with a central 30-2 threshold test. Such referral criteria have been reported as having a sensitivity of 95% and a specificity of 80% to detect glaucomatous visual field defects[24] Diagnostic criteria for glaucoma were selected to include only established cases where the diagnosis was not in question. This definition would thus provide a minimum estimate of glaucoma prevalence. For the purposes of the pilot study definite glaucoma was diagnosed in the presence of intraocular pressure >24 mmHg and optic nerve damage, as shown by a definite abnormality of the disc on clinical examination (horizontal or vertical cup-disc ratios were ≥0·7) and visual field defects confirmed by retesting. Participants who did not meet all the criteria for definite glaucoma diagnosis were considered as glaucoma suspects.

The prevalences of age related cataract, macular degeneration, and diabetic retinopathy were determined by clinical examination. The diagnosis of age related cataract was based on the presence of lens opacities with a visual acuity loss of 20/30 or worse in the absence of other apparent causes. To guide the examiner in diagnosing macular degeneration and diabetic retinopathy standard photographs were provided.[25,26]

The diagnosis of hypertension was based on a blood pressure >160/95 mmHg (average of two measurements) and/or a history of antihypertensive treatment. The diagnosis of diabetes was based on self-reported history. Since it was not possible to perform fasting blood glucose tests in the pilot study, all persons were screened for glycosuria and those found positive were referred for further examination. A 10% sample of persons with negative tests were asked to return for a fasting blood glucose test. This was done in an attempt to identify false negatives, since glycosuria screening has low sensitivity.

Results

The pilot study lasted three months, a time span which allowed contacting all but the last 48 persons in the sample. Of the 252 persons contacted 89·3% were eligible to participate and the rest were ineligible for the reasons shown in Table 1. Of the eligible persons

Table 1 *Eligibility to participate in the pilot study*

	Number	
Contacted	252	
Eligible		225 (89·3%)
Could not participate		27 (10 7%)
Deceased		6
Seriously ill		6
Senile		3
Absent (overseas)		12
Not contacted	48	
Total	300	

95% agreed to participate; there was no variation in participation by geographic region (Table 2). Data collection was completed for 193 persons in the time available. A comparison of the distribution by age, sex, and race (as recorded by interview) of the participants with that reported by the 1980 census shows very good agreement (Table 3). The pilot study examinees were therefore similar to the general population in those background variables.

According to the study definitions 12 persons (seven males, five females) were found to have definite open-angle glaucoma and 17 persons (seven males, 10 females) suspected glaucoma. All the cases of definite glaucoma were among persons of African descent, giving an overall prevalence of 6·9% in this group (Table 4). As regards age specific prevalences in black and mixed participants, 11 of the 12 cases were in persons >54 years, giving a prevalence of 12·8% in this age group. The prevalence of suspected glaucoma was about 9% (Table 4). Intraocular pressures over 21 mmHg were found in 9% and 12% of right and left eyes respectively and tensions over 24 mmHg in 5% and 7%.

The prevalences of age related cataract, macular degeneration, and diabetic retinopathy by clinical examination were 26%, 3%, and 5% respectively (Table 5). A high prevalence of hypertension and diabetes was found in this population. Among black and mixed persons >54 years 59% had hypertension and 21% had been diagnosed as diabetics (Table 6); two-thirds of these diabetics had glycosuria.

Discussion

The pilot study results showed that the sampling method used was feasible, and most persons identified were eligible to participate (Table 1). The participation was high in all areas of the country, with an overall participation rate of 95% (Table 2). The age, sex, and race distributions of pilot study participants were comparable to those found in the 1980 census (Table 3), thus suggesting an adequately representative population for these variables. For all these reasons the effect of any possible biases related to non-participation is likely to be small.

The pilot study examination showed a high prevalence of open-angle glaucoma among Barbadians of African descent (Table 4), especially at older ages. The small number of people examined precludes any conclusions regarding the true prevalence of glaucoma and other eye diseases in the sample, since the number of persons with such conditions was small (Table 5). Hypertension was a frequent finding in the pilot study (Table 6), as in other black populations. The prevalence of self-reported diabetes was 13% (Table 6). Because the pilot study did not perform

Table 2 *Participation of eligible persons by region*

	Region			
	I	*II*	*III*	*Total*
Eligible to participate	70	83	72	225
Agreed	67	78	68	213
Refused	3	5	4	12
Percentage participation	96	94	94	95

Table 3 *Percentage distribution of age, sex, and race in 193 pilot study participants versus the 1980 census*

Age (years)	*Participants (%)*	*1980 Census (%)*
35–44	27	24
45–54	25	25
55–64	20	20
65–74	17	20
75+	12	11
Sex		
Females	56	54
Males	44	46
*Race**		
Black	88	89
Mixed	5	6
White	5	4
Other	2	1

*Excludes 5 persons with missing data

Table 4 *Age specific prevalence of definite and suspect glaucoma in black and mixed participants*

Age group		*Definite glaucoma*			*Suspect glaucoma*		
	n	*n*	%		*n*	%	
35	45	1	2·2		2	4·4	
45–54	43	0	0·0		3	7·0	
55–64	34	3	8·8		4	11·8	
65–74	32	6	18·8	12·8%	3	9·4	12.8%
75+	20	2	10·0		4	20·0	
Total (mean %)	174	12	6·9		16	9·2	

Table 5 *Clinical diagnoses of cataract, macular degeneration, and diabetic retinopathy by age and race*

Age, race	*n*	*Cataract*		*Macular degeneration*		*Diabetic retinopathy*	
		n	%	*n*	%	*n*	%
Black and mixed							
35–54 years	88	2	2	0	0	4	4
>54 years	86	43	50	5	6	5	6
All		45	26	5	3	9	5
White and other							
35–54 years	7	0	0	0	0	0	0
>54 years	7	4	57	1	14	0	0
All		4	29	1	7	0	0
All races							
35–54 years	95	2	2	0	0	4	4
>54 years	93	47	50	6	6	5	5
All		49	26	6	3	9	5

Table 6 *Hypertension and self-reported diabetes by age and race*

Age, race	*n*	*Hypertension*		*Diabetes history*	
		n	*%*	*n*	*%*
Black and mixed					
35–54	88	25	28	4	4
>54 years	86	51	59	18	21
All		76	42	22	13
White and other					
35–54 years	7	1	14	0	0
>54 years	7	2	28	2	28
All		3	21	2	14
All races					
35–54 years	95	26	27	4	4
>54 years	93	53	57	20	22
All		79	42	24	13

blood testing for glucose on everyone, the true prevalence of diabetes is probably higher, a conclusion supporting the clinical impressions of a high diabetes frequency in this population.

The study reported here was a pilot investigation that was not designed to provide prevalence estimates for glaucoma or other conditions. The data suggest, however, that open-angle glaucoma is very frequent in Barbados (Table 4), a result that merits further study.

There is no clear explanation for an increased glaucoma risk in black populations. This increased susceptibility may be related to the somewhat higher intraocular pressure in blacks than whites.[27] Although the reason for this increased intraocular pressure is not known, it might be at least partly related to the higher blood pressure, larger body size, and darker iris pigmentation of blacks than whites. All these variables have been associated positively with intraocular pressure in various population based studies.[27-29] The differences in intraocular pressure between black and whites, however, are not large, and other variables probably contribute to their differences in glaucoma risk.

An increased severity of glaucoma among blacks could be due to a poor response to treatment in heavily pigmented eyes. While this clinical observation can explain a high risk of blindness among blacks who already have glaucoma, it does not account for an increased incidence of the disease. Other factors that could also explain an increased visual impairment from glaucoma among blacks include limitations in access to glaucoma treatment and/or poor compliance to prescribed treatment. Although these variables could affect disease severity, they would not be related to incidence.

In sum, despite the reported high glaucoma risk for blacks, the reasons for the increased risk are unknown. There is clearly a great need for investigations which are designed to examine these issues and to provide data for blindness prevention programmes. The pilot study described here represents a first step towards implementing such an investigation.

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A net for extending the optic nerve at enucleation of the eyeball

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SUMMARY A long section of optic nerve can be obtained during enucleation, when the eyeball is caught in a net made specifically for this purpose. The net is knitted from surgical thread and is in the shape of a barrel with two openings: one wide, one narrow. Separate thread is wrapped around the edge of the wide opening. When the eyeball is freed from the extrinsic muscles and Tenon's capsule, it is drawn into the net, and the wide opening is closed round the optic nerve. At the narrow opening there are three slip-knots by which the net is pulled forward and out of the orbit. Then the optic nerve is exposed and the surgeon is able to cut it close to the apex of the orbit. The length of severed optic nerve amounts as a rule to about 15 mm or more, depending on the age of patient.

The indications for enucleation of the eyeball are numerous, and it is an operation which must be performed frequently. In cases of intraocular malignancy enucleation may save the patient's life. In standard procedures the excising of enough length of the optic nerve presents a distinct problem. Often the surgeon cannot judge accurately the length of nerve exposed, and hence cutting is done at random. Grasping the globe by the remnants of one or more extrinsic muscles as well as using various curettes[1] to extend the optic nerve do not give satisfactory results. The eyeball is not sufficiently separated from the adjacent tissues of the orbit by these means and the optic nerve cannot be seen.

In practice I have used all such curettes and slip-knots and tried out slip-knots which I made myself, but the results have not been very successful. Again the globe and adjacent tissues disturbed the final step in the enucleation. To overcome these problems I have developed a net which is capable of enclosing the entire eyeball and allowing accurate excision.

Material and methods

The net is knitted from surgical linen thread (no. 100) with rectangular openings. Its length is about 25 mm and its width at the centre about 35 mm. There are two openings into the net: one with a diameter of 30 mm and one with a diameter of 20 mm. Stronger thread (no. 90) is wrapped round the wider opening. This thread serves to close the net about the optic nerve when the globe is inside. Three slip-knots are tied at the narrow opening to act as a handle, and on pulling them the net with the eyeball inside is pulled out from the orbit (Fig. 1). The dimensions of the net

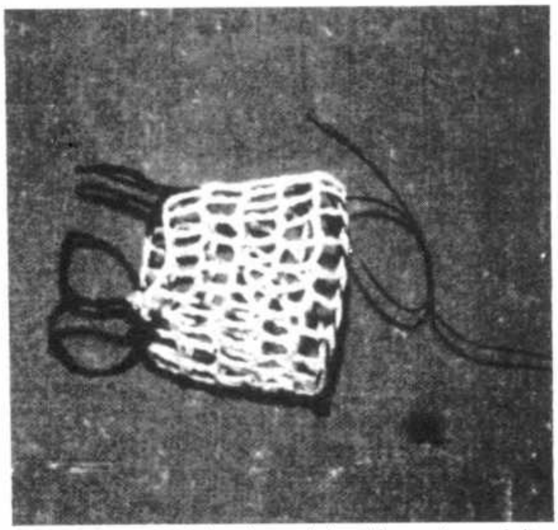

Fig. 1 *The net with thread round the wide opening and slip-knots on the narrow opening.*

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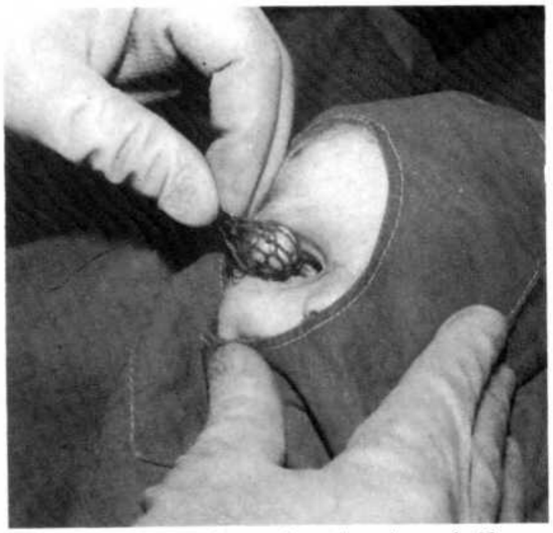

Fig. 2 *Enucleation of an eye from the cadaver of a 12-month-old child. The eyeball is completely drawn into the net.*

are somewhat larger than those of the eyeball and can be varied about 2 mm. If the eye which has to be enucleated is buphthalmic or swollen, lateral canthotomy can be performed so that the work of enucleation is made easier.[2]

At present the net is not produced commercially. The prototypes have been produced by my wife using an ordinary crochet needle. I am hoping to obtain its commercial production.

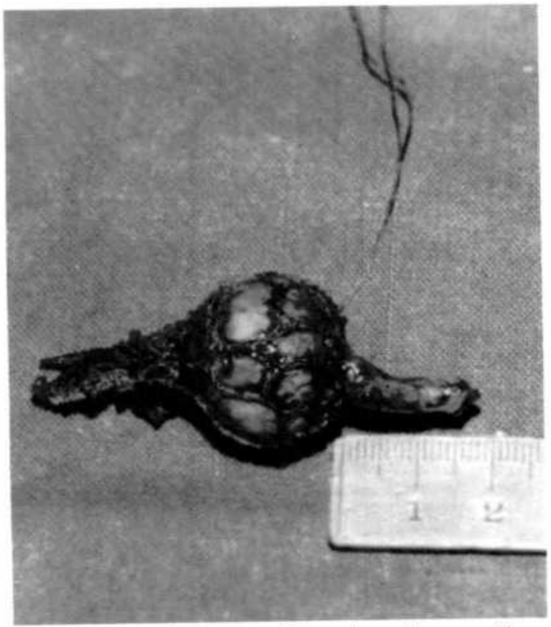

Fig. 3 *A severed optic nerve 17 mm long of an eye with retinoblastoma.*

Until the severing of the optic nerve the procedure of enucleation is performed in the classical way.[2] When the eyeball is freed from the extrinsic muscles and the Tenon's capsule, it is drawn into the net through its wider opening. At this point the wider opening is closed through the surgeon stretching and tightening the thread and the globe is caught in the net. In the next step the surgeon catches the slip-knots at the narrow opening and slowly pulls the net forward and temporally (Fig. 2). An assistant with a steel retractor draws the soft tissues of the orbit nasally, and the surgeon can observe part of the optic nerve. The optic nerve is approached from the nasal side because the foramen opticum is situated nasally and a little above the orbital apex. The surgeon now presses the closed enucleation scissors back to the optic foramen, opens the blades, and cuts the nerve at the level of the foramen. As a result of this procedure the enucleated eye generally presents a length of optic nerve of about 15 mm in children and more in adults (Fig. 3).

Discussion

The intraorbital part of the optic nerve amounts to about 17 mm in the newborn infant, and its length increases until the age of 12, so that in adults it reaches 25 to 33 mm.[3-5] At enucleation it is necessary to cut the optic nerve as far behind the globe as possible. This is especially so in cases of intraocular malignancies such as retinoblastoma. This tumour of neural origin travels along the optic nerve, invading intracranial structures and the bones of the skull, and spread of a tumour into the orbit after enucleation mostly comes from the stump of the optic nerve.[6] Therefore the globe needs to be enucleated together with the orbital part of the optic nerve.

The standard procedures for pulling the globe and putting the optic nerve under tension do not give the best results. The nerve is often cut near the sclera or a few millimetres from it. This is because thickened connective tissue frequently persists round the dural sheath of the optic nerve at its junction with the globe. This has been noted by Havre[7] and has been my observation too, working on both cadavers and patients. This connective tissue prevents the surgeon from pushing the enucleation scissors back to the apex of the orbit. Furthermore the surgeon may accidentally cut the adjacent orbital tissues instead of the nerve and haemorrhage occurs, which considerably prolongs the operation.

Having used the net, which I have been developing over the past two years, I have found it has effectively

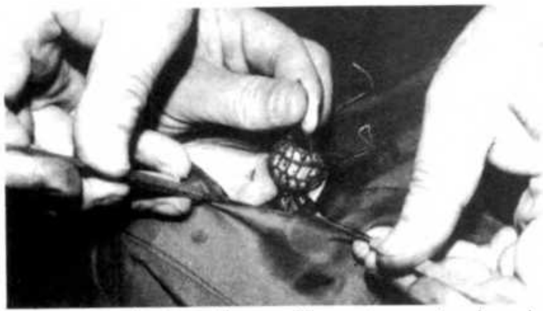

Fig. 4 *Enucleation with a net. The optic nerve is enlarged between the sclera and the optic foramen.*

eliminated all the difficulties which arise during the standard procedures. Exposing the optic nerve in this way best allows the section to be performed under the control of the surgeon, who can always estimate how much of the nerve's length is being severed. If there is additional connective tissue round the optic nerve, it can be liberated better when the globe is drawn into the net, as the whole of the retrobulbar space can be clearly observed. In such a way the net can be drawn up partially at first and entirely later. Thus the risk of cutting adjacent tissues is diminished, and in this way additional bleeding is prevented. Furthermore, the scissors can be moved up to the apex of the orbit without hindrance.

As well as being used effectively in cases of intraocular malignancy the net proved to be especially efficient with one of our patients with astrocytoma of the optic nerve. The eye of this girl of 6 was protruded; her visual acuity was no perception of light; and oedema of optic disc could be seen. Examination showed a tumour of the optic nerve, and it was decided to enucleate the eye, with the complete section of the nerve. The net was used, and after the eyeball was pulled the swollen optic nerve could be seen (Fig. 4), which was then cut at the optic foramen. Histological examination showed an astrocytoma of the optic nerve.

I consider that this simple method will find its place in the operating room, making all work on the enucleation of the eye safe.

I am most grateful to Drs Alush Gashi and Hashim Maloku for the opportunity to perform many examinations with the net on cadavers.

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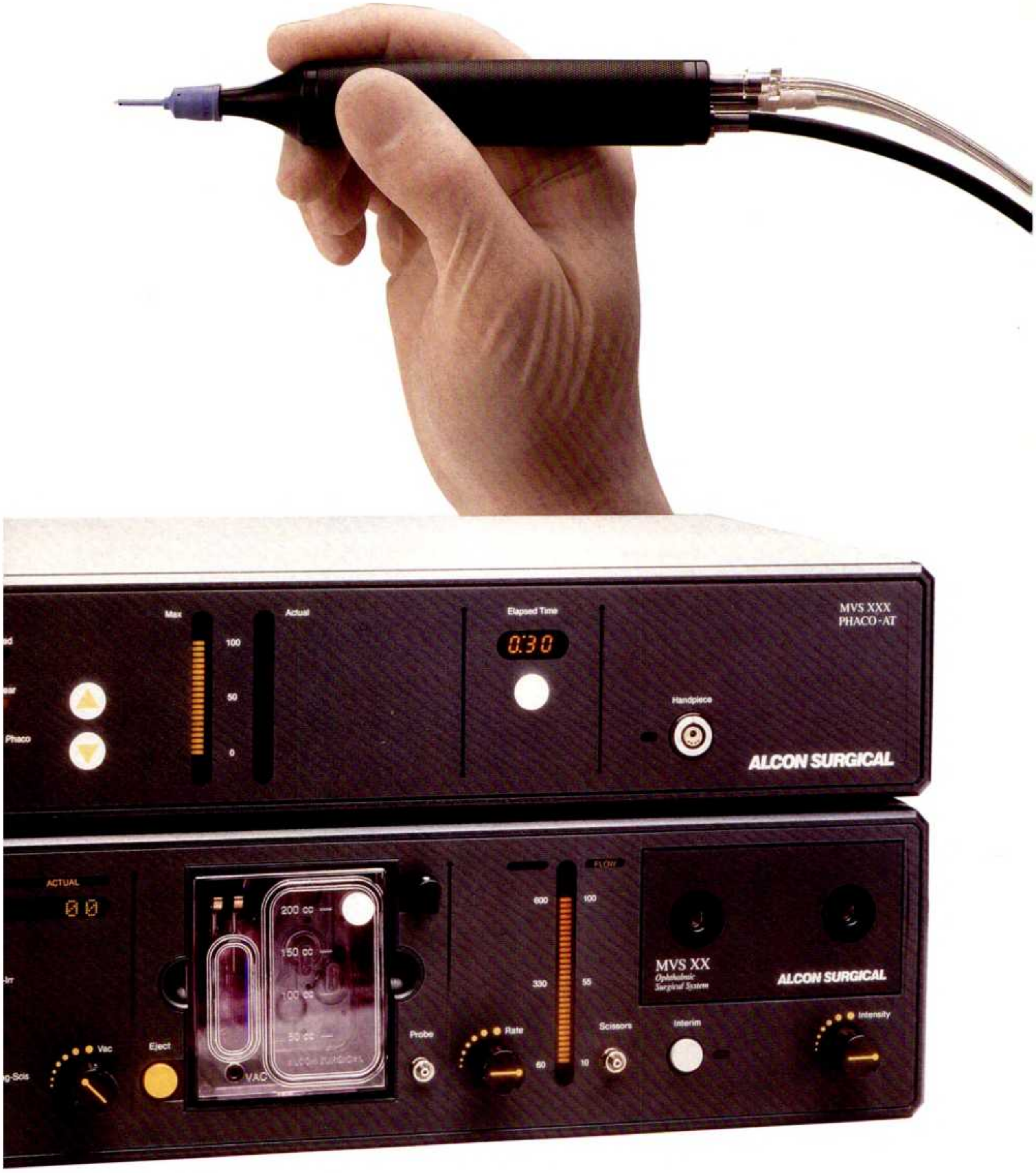

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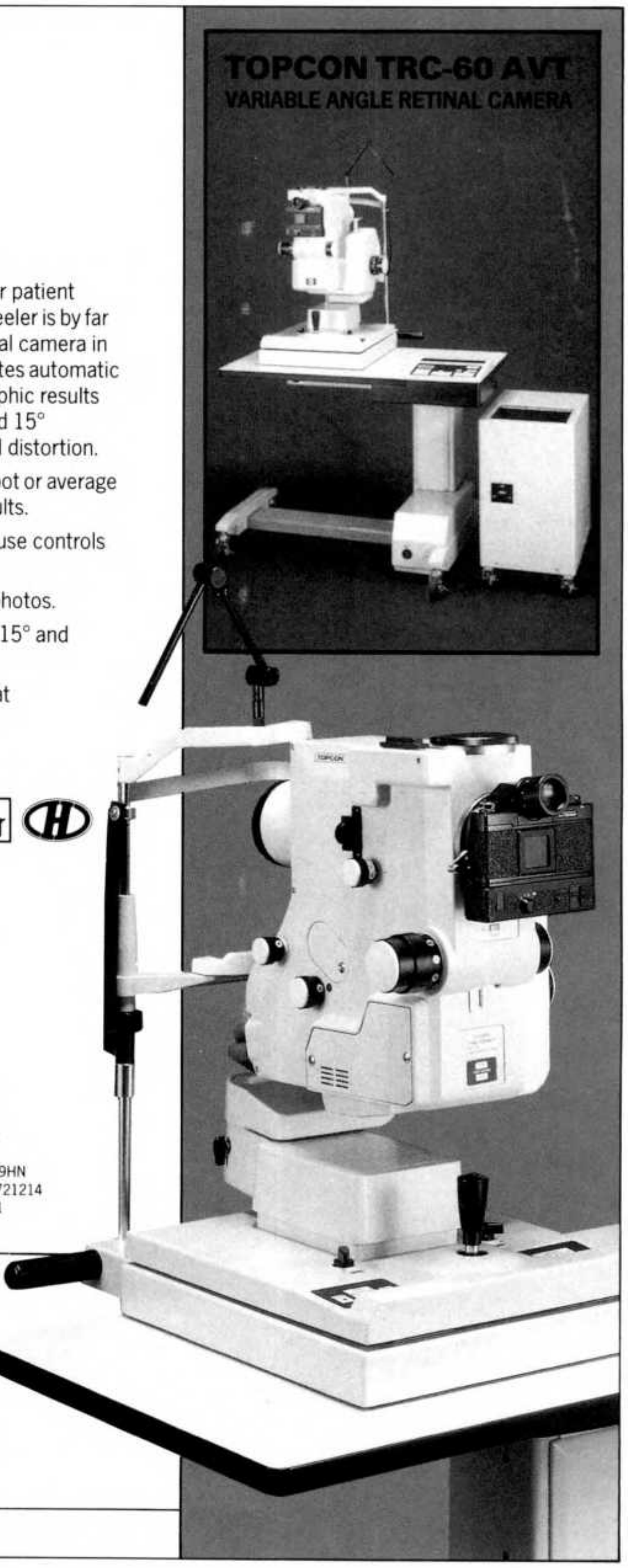

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British Journal of Ophthalmology, 1989, **73**, 373–375

Adult periorbital fibromatosis

CATHERINE N SMOOT, GREGORY B KROHEL, AND RICHARD S SMITH
From the Department of Ophthalmology, Albany Medical College, New York

SUMMARY Three patients aged 15 to 40 years with fibromatosis of the periorbital region were studied. A history of acute onset, preceding trauma, and pain associated with a palpable mass were typical features. Rapid recurrence followed surgical excision. Misdiagnosis is common in this benign disease and may lead to unnecessary examinations for malignancy. Surgical excision or debulking of these masses is indicated for diagnosis and pain relief, but long-term follow-up indicates that these lesions will often spontaneously resolve with time.

Benign acute recurrent fibromatosis is a fibroblastic proliferation that lies in a range between normal repair with scar formation and fibrosarcoma. Reports have suggested that trauma may play a part in the development of this disease,[1] though other reports dispute this connection.[2-4] These fibrous masses have no definable margins and may locally invade bone and striated muscle. They do not tend to metastasise.[3 5 6] The pathological diagnosis may be confusing and malignancy is often initially suspected.

Juvenile fibromatosis is a well described clinical entity that occurs throughout the body, though the abdomen appears to be the most frequent site.[1] Fibromatosis of the periorbital region has previously been described in children.[4] Clinical characterisation of this entity in adults has not been described in the ophthalmic literature. We recently treated three women with recurrent periorbital fibromatosis

Case reports

A 24-year-old nursing student first presented to Albany Medical Center Hospital (AMCH) in January 1984 with a corneal ulcer refractory to treatment. She developed ecchymosis, swelling, and warmth of the left infraorbital region while in the hospital. This appeared to respond to intravenous antibiotic therapy, though a small nodule remained over the left premalar area. In April the patient was noted to have increasing ecchymosis of the left lower lid and premalar region. An excisional biopsy via a subciliary eyelid incision revealed diffuse fibrotic tissue over the premalar area and extending into periosteum. The initial pathological interpretation was rhabdomyosarcoma and an oncology specialist was consulted. Re-examination of the specimen suggested a reactive myositis.

One month later the patient presented with a painful ecchymotic mass and a small eschar in the premalar region. A second biopsy was obtained and a diagnosis of fibromatosis was made. In October of 1984 the eschar enlarged and she underwent drainage of an abscess over the left malar eminence. Manipulation of the wound site by the patient was suspected and she was referred to the psychiatric service for evaluation of probable Munchausen's syndrome[7] Her clinical course improved slowly under psychiatric observation. No recurrence of her problem has been noted over the past two years.

CASE 2

A 15-year-old female presented to AMCH in May 1981 with a history of spontaneous left malar and infraorbital ecchymosis. It was later thought she might have suffered injury from her boyfriend. A painful, palpable, ecchymotic mass was noted along the left inferior rim (Fig. 1). A subciliary excisional biopsy was performed and initially interpreted as nodular fasciitis. Further review and consultation with the Armed Forces Institute of Pathology confirmed the diagnosis of benign fibromatosis The patient experienced several recurrent episodes of painful ecchymosis, with regrowth of the mass. A repeat anterior orbitotomy performed six months later confirmed the diagnosis of fibromatosis. Over the next three years she had several episodes of painful swelling and ecchymosis lasting one to two weeks. Each recurrence tended to be less severe and resolved spontaneously. Further surgery was not necessary.

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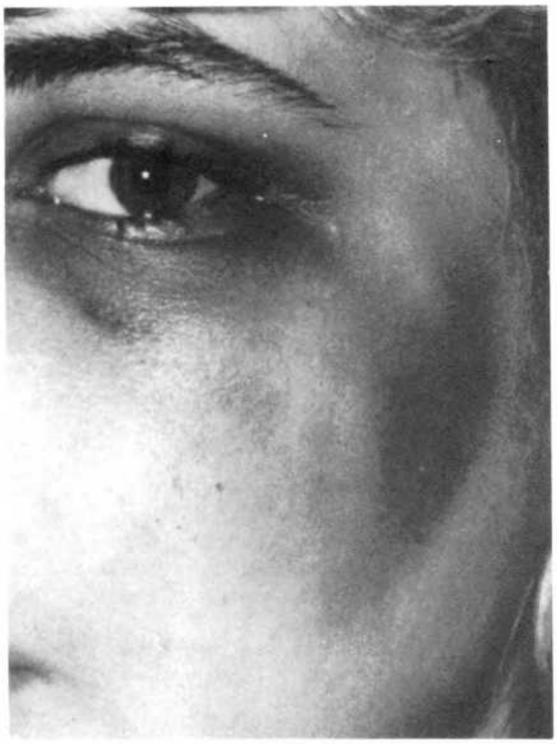

Fig. 1 *Ecchymotic mass over the left infraorbital and malar area secondary to fibromatosis.*

CASE 3

A 40-year-old nurse was accidentally struck forcefully in the left infraorbital area by a patient's head in November 1986. This resulted in persistent, painful infraorbital swelling over the left malar area accompanied by a dimpled contracture. Two months later a fibrotic mass was removed by anterior orbitotomy through a subciliary incision. Pathological examination confirmed the clinical diagnosis of fibromatosis. Two weeks postoperatively she presented with a recurrent painful mass. The decision was made to institute massage therapy with vitamin E cream while observing the clinical course. The dimpling and pain had decreased four months later. A small pea sized nodule remained. By September 1987 the dimpling and pain had resolved, and only a small soft nodule over the left lateral premalar area remained. No further surgery is planned.

Discussion

Fibromatosis in adults and children has been previously described in various sites of the body including the periorbital region.[1,3,4,8,9] Our three cases of adult periorbital fibromatosis had several features in common. Two patients had a definite history of trauma immediately preceding the onset of the lesion and trauma was strongly suggested in the third case. Trauma has been mentioned as an aetiological agent in some cases of fibromatosis,[1] though five of six patients previously described with juvenile periorbital fibromatosis had no history of trauma.[4] Despite the ecchymotic appearance of these lesions haemosiderin was observed in only one of our three patients.

All three patients in our series were women. A female preponderance had been noted previously, suggesting a hormonal influence in the development of fibromatosis.[8]

The prevalence of pain with fibromatosis remains uncertain. Conley *et al.*[3] noted an absence of pain in seven patients with periorbital lesions, while two patients with periorbital lesions in another series had associated pain.[8] The onset of symptoms was acute and painful in the three patients we treated. This contrasts with the cases of juvenile periorbital fibromatosis previously reported in the ophthalmic literature which were described as firm, painless lumps, with no mention of acute onset.[4]

Misdiagnosis of this benign tumour can occur.[9] One of our patients underwent examination for suspected rhabdomyosarcoma. The other misdiagnoses in our patients were reactive myositis and nodular fasciitis.

A surgical approach via a subciliary incision in all three patients yielded excellent postoperative cosmesis (Fig. 2). A firm, whitish rubbery mass extending from subcutaneous tissue to periosteum was observed in all cases. Integrity of the surrounding

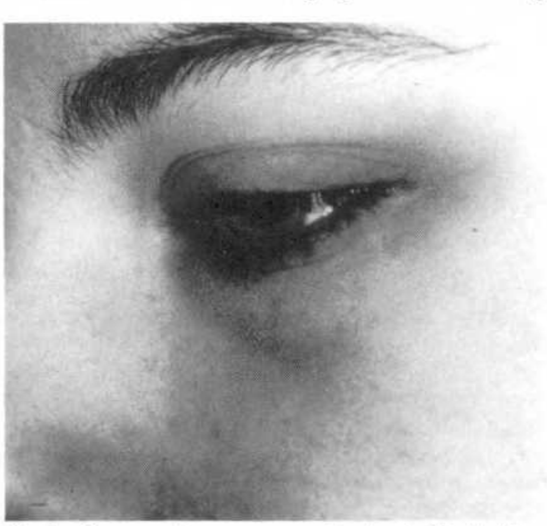

Fig. 2 *Postoperative appearance of patient in Fig. 1 with a good cosmetic result. The patient had several recurrences following surgery.*

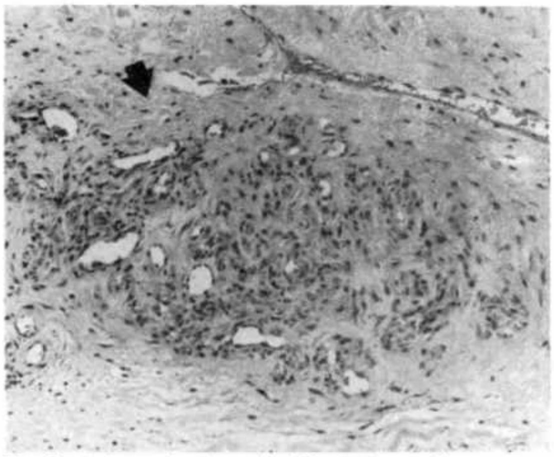

Fig. 3 *A focus of perivascular fibrous tissue with lymphocytic infiltration (arrow) consistent with fibromatosis. (Haematoxylin and eosin ×150).*

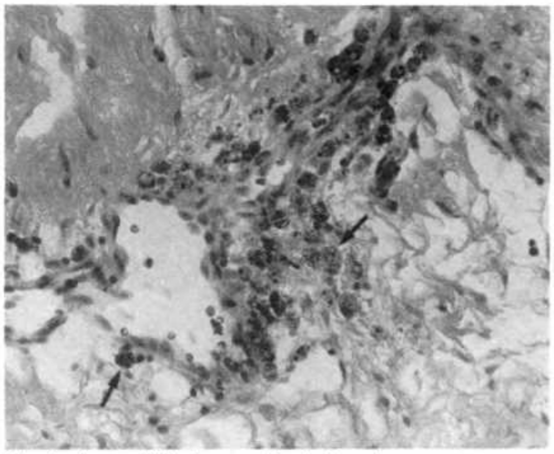

Fig. 4 *Intracellular haemosiderin deposits are present (arrows). Haemosiderin was noted in only one of three patients despite the ecchymotic appearance of all three lesions. (Haematoxylin and eosin, ×60).*

bony structures was preserved in two cases, though local bony invasion similar to that previously reported was observed in one patient.[3]

Histopathologically, fibromatosis is a proliferation of fibroblasts with interstitial collagen and rare mitotic activity.[9] This differs from fibrosarcoma which has less interstitial collagen and more mitotic activity.[10] Hidayat and Font[4] microscopically noted a leiomyomatous appearance of the tumours in three of the juvenile patients they reported, a picture similar to that of congenital generalised fibromatosis. Our pathology sections showed dense perivascular collections of fibrous tissue with frequent foci of lymphocytes in all specimens (Fig. 3). The fibroblastic cells varied in shape from spindle to stellate, while nuclei differed in their size and degree of basophilic staining. Haemosiderin was noted in the pathological specimens in one case (Fig. 4). Electron micrographic (EM) studies confirmed the fibroblastic nature of the lesion in one patient. Characteristic features shown included a proliferation of mesenchymal fibroblasts with an increase in rough cytoplasmic reticulum and the presence of intercellular fibrin and collagen.

The treatment employed was local surgical excision of the lesion. The therapeutic value of steroids,[6,11] radiation,[3,12] or chemotherapy[13] remains inconclusive. Despite good surgical results all our patients had recurrences. We decided to reoperate only if the pain could not be controlled medically. Two of our three patients required further surgery for that reason, while one was successfully managed with time and massage after the initial resection.

In summary, benign acute idiopathic fibromatosis should be considered in the differential diagnosis of acute, tender, palpable periorbital lesions in adults. A careful history may reveal a preceding traumatic incident. Surgical excision affords local pain relief and cosmetic improvement, but recurrences are common.

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A case of aberrant lacrimal gland and fistula

GÜLCAN KURAL, ARIF SERIFOĞLU, AND SAADET ERTÜRE

From the Numune Hospital, Ankara, Turkey

SUMMARY A case of aberrant lacrimal gland and fistula sited extraorbitally is presented in view of its rare incidence.

An aberrant lacrimal gland is a rare abnormality. We report here a case observed in the Clinic of Ophthalmology, Numune Hospital, Ankara.

Case report

A 9-year-old boy was seen in September 1987 with the complaint of constant watering since birth from the middle of the right temporal region, where the skin was never free of tears. The watering increased on weeping.

On examination, a small orifice could be seen in the skin in the middle of the right temporal region. The opening was round and 1 mm in diameter. Clear transparent fluid could be seen continually flowing from the orifice (Fig. 1). There was no evidence of excoriation, inflammation, or swelling round the opening. Apart from this condition both eyes, including the lacrimal apparatus, were normal in all respects. There was no other congenital abnormality in the eyes or elsewhere.

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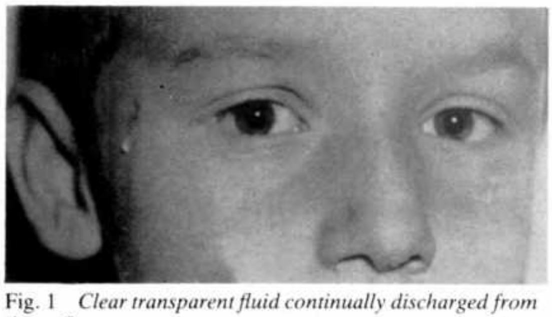

Fig. 1 *Clear transparent fluid continually discharged from the orifice.*

A quantitative biochemical assay of the transparent fluid coming from the orifice, which was consistent with that of tears, was done. A fine catheter could be passed into the fistula for about 0·5 cm in the direction of the external canthus. Radiological examination after injection of radio-opaque dye showed the dye in the fistula. The investigations confirmed that the fluid coming from fistula was tear secreted by an aberrant lacrimal gland.

The patient was operated upon. After skin incision had been made and a probe passed, the fistula and the gland, which was $0{\cdot}5\times0{\cdot}8\times1{\cdot}6$ cm in size, were dissected out from the surrounding tissues. The gland with the fistula was completely removed. The postoperative course was normal.

Microscopic examination of the specimen showed a glandular tissue similar to that of lacrimal gland (Fig. 2).

Discussion

An aberrant lacrimal gland is an unusual congenital and developmental abnormality and differs from an ectopic gland.[1] The first case of aberrant lacrimal gland associated with other congenital abnormalities was reported by Gördüren in 1962 in Turkey,[2] and in 1963 a second case was also reported by the same author.[3] Firat and Emüler[4] described two cases of aberrant lacrimal gland in the bulbar conjunctiva. Slem *et al.* reported a case of aberrant lacrimal gland in the orbit.[5] Our case is a typical example of an aberrant lacrimal gland, and we believe it to be the sixth case from this country to be published.

Dr Ayşe Ayhan examined the sections of the specimen and we are indebted to her for the histopathological diagnosis.

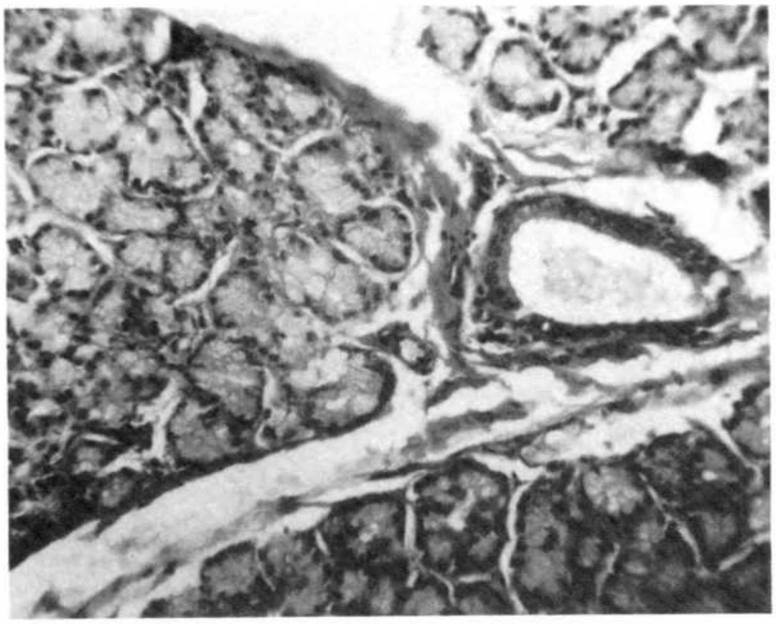

Fig. 2 *Glandular acini observed in the microscopic sections. (Haematoxylin and eosin, ×240.)*

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Intrascleral neurilemmoma

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SUMMARY The case of an anteriorly situated, intrascleral, neurilemmoma in an 11-year-old girl is reported. Only two similar cases have been described in the literature, and the diagnosis was made only after detailed histological examination, including electron microscopy and specialised staining techniques, to differentiate a neurilemmoma (schwannoma) from a neurofibroma.

Neurilemmomas are benign, encapsulated tumours composed of proliferating Schwann cells, usually unassociated with neurofibromatosis. They arise from ciliary nerves in the orbit and account for about 1% of primary orbital tumours.[1]

Shields *et al.*[2] in 1981 reviewed the literature for solitary nerve sheath tumours of the globe and found 17 (including the one they described) involving the uveal tract and three involving the sclera. The average age of those patients with uveal tumours was 37, with a female:male ratio of 3·6:1. Only two of the 17 were associated with neurofibromatosis. These authors pointed out, however, that many of the cases reported had not been investigated by modern histological techniques and that it was impossible to state with certainty whether the tumours were neurilemmomas or neurofibromas. When Rosso *et al.*[3] considered these cases, they believed only six to be proved neurilemmomas.

Neurilemmomas derived from ciliary nerves in the sclera occur even more rarely than in the uveal tract. One tumour has been described situated posteriorly in a 76-year-old female, in whom it simulated an orbital tumour,[4] and two cases of limbal neurilemmomas occurring in a 14-year-old female and a 12-year-old male have been reported in the older German literature.[5 6]

Case report

An 11-year-old Cypriot girl presented to the Casualty Department in July 1981 with a one-month history of a small lump in the upper part of her left eye. On examination the visual acuity was 6/5 unaided, and two small, apparently separate masses were noted in the superotemporal aspect of the globe just posterior to the limbus. No other abnormality was detected, and a full blood count and differential white cell count performed at that time were normal. A decision was made to withhold surgery until the masses caused symptoms.

Over the next three years the masses enlarged, and by the time she returned in July 1984 requesting surgical treatment they were clearly parts of the same

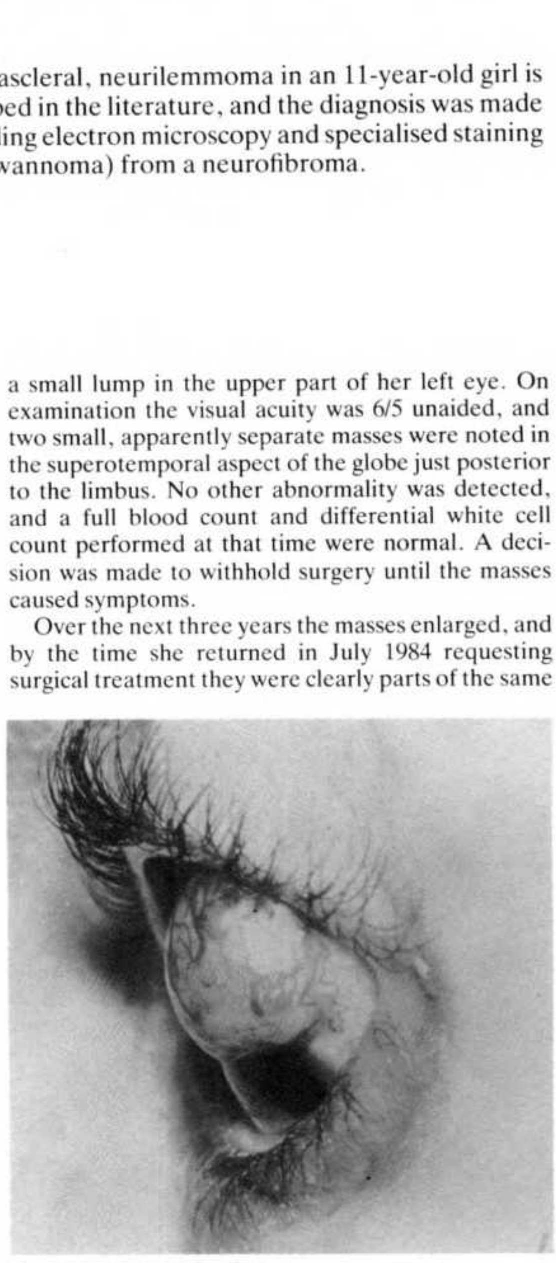

Fig. 1 *Eyelid raised to demonstrate tumour.*

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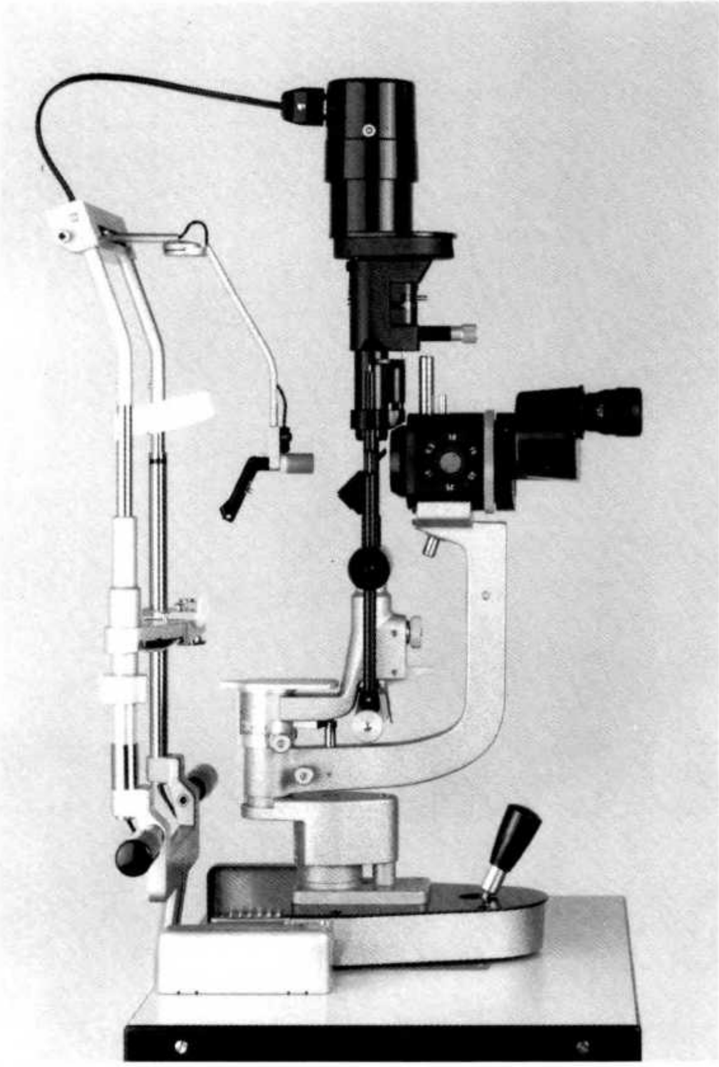

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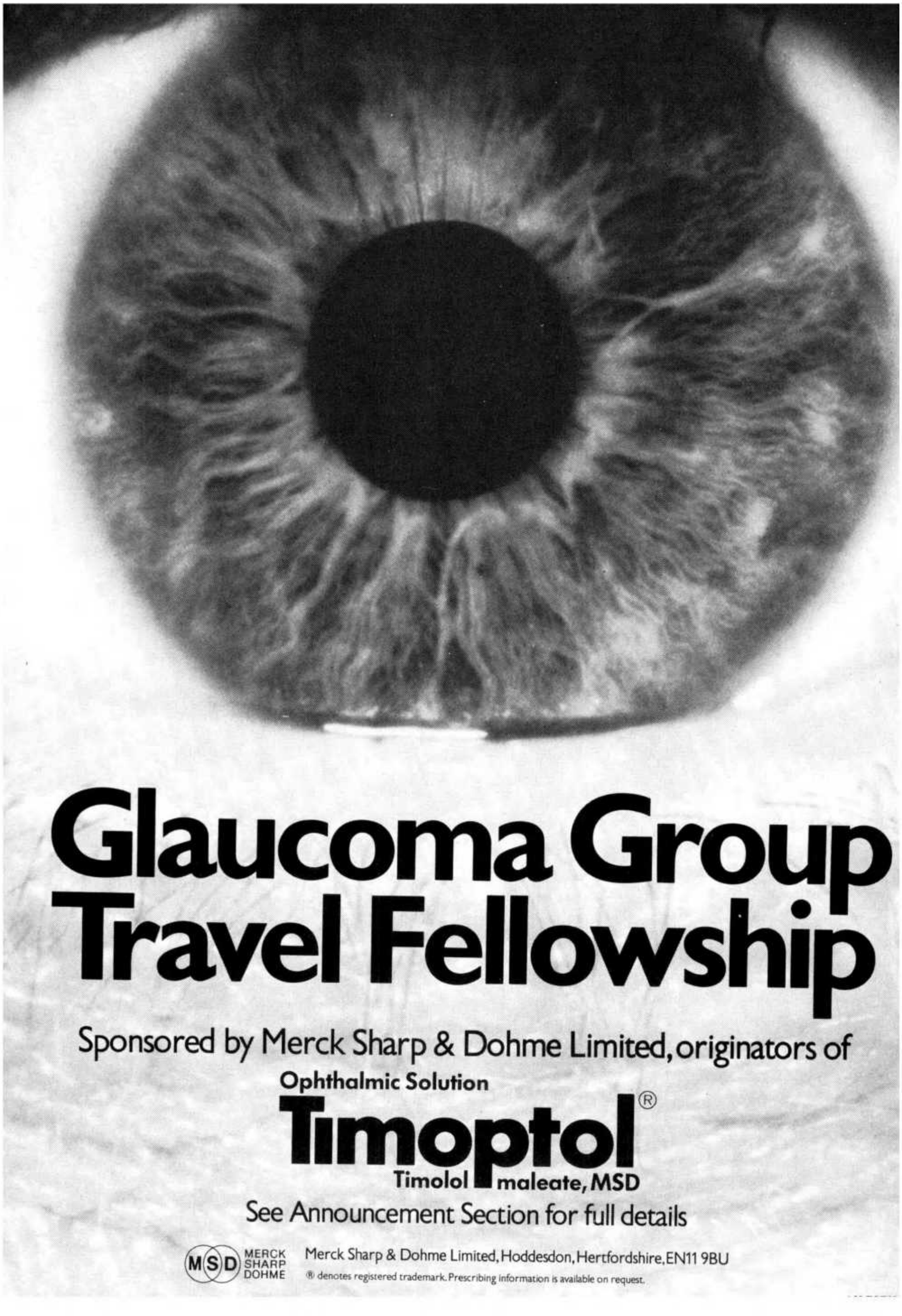

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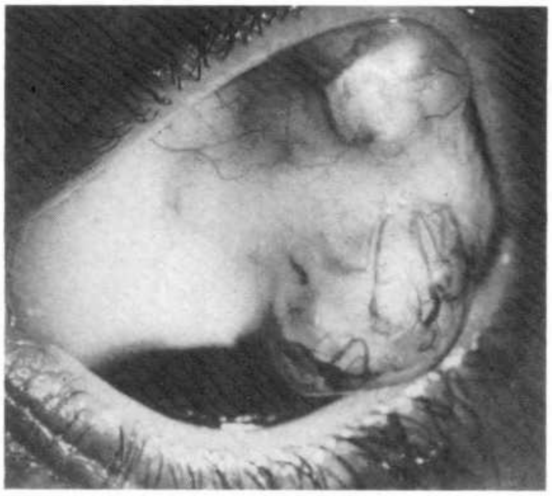

Fig. 2 *Demonstration of dumb-bell contour of tumour.*

lesion. The visual acuity was 6/6 unaided and she had developed a mechanical ptosis.

By June 1985 the eye had become uncomfortable, the ptosis had increased to 3 mm, with the contours of the lump visible through the upper lid, and the mass had noticably enlarged (Figs. 1, 2). The superior part of the cornea had become distorted, and fundal examination revealed a deep indent corresponding to the external position of the posterior part of the mass. General physical examination did not suggest any underlying systemic disease, and serological tests for parasitic infections were negative. An ultrasound examination showed the mass to be solid.

In October 1985 the tumour was excised under general anaesthetic. Highly vascular conjunctiva was readily separated from the underlying, well encapsulated mass, which in turn was separated from the globe by blunt dissection to reveal a patch of partial-thickness sclera with a large area of bare choroid centrally. Minimal manipulation led to rupture of the globe, and it was necessary to close the defect with donor sclera.

The postoperative course was uneventful, and when she was last seen in the summer of 1987 the patient was asymptomatic.

PATHOLOGY

The dumb-bell shaped tumour measured 19×7×7 mm. There was a hyalinised connective tissue capsule round the vacularised tumour, which consisted of intertwining fascicles of spindle cells showing little pleomorphism. In some areas there was palisading of nuclei (Fig. 3) and in others myxoid degeneration. Collagen deposition was marked (Fig. 4). The differential diagnosis included fibroma, neurofibroma, and neurilemmoma. No axons were demonstrable within the substance of the tumour on immunohistochemical staining with antineurofilament protein antibody, but the S-100 stain was strongly positive in the spindle cell areas. Electron microscopy showed Lüse bodies (Fig. 5) between cells with flattened and invaginated nuclei; microfibrils were present within the cytoplasm with occasional lysosomes and mitochondria.

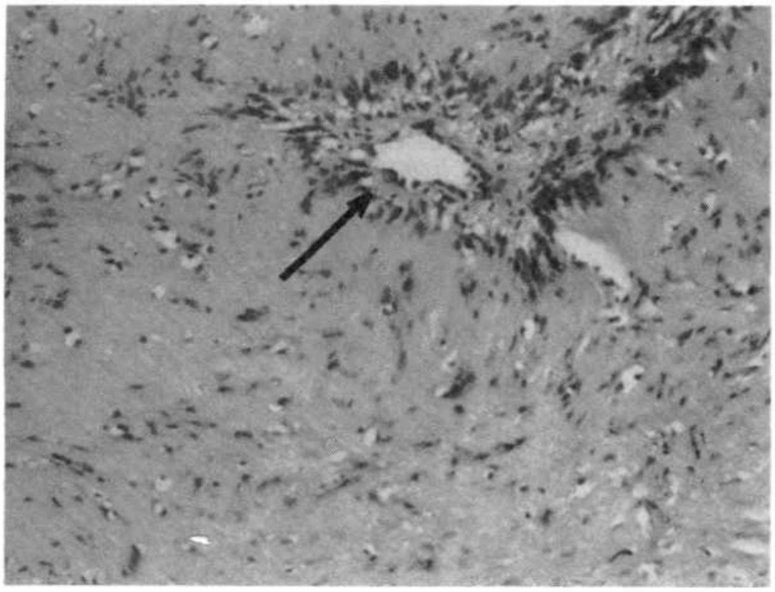

Fig. 3 *Palisaded nuclei (arrowed) in spindle area of tumour. (H and E, ×180.)*

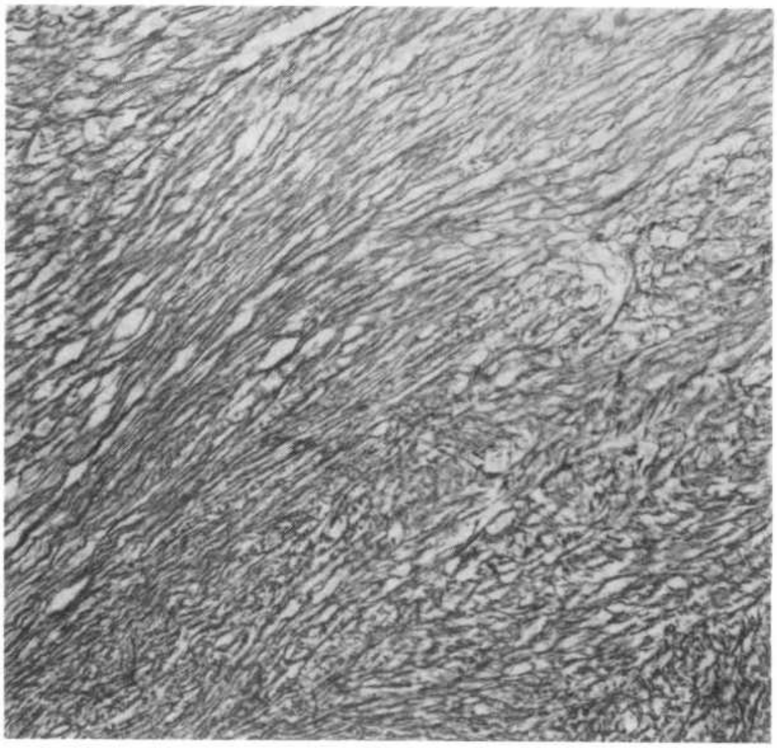

Fig. 4 *Extensive reticulin framework present within the tumour. (Silver preparation, ×180.)*

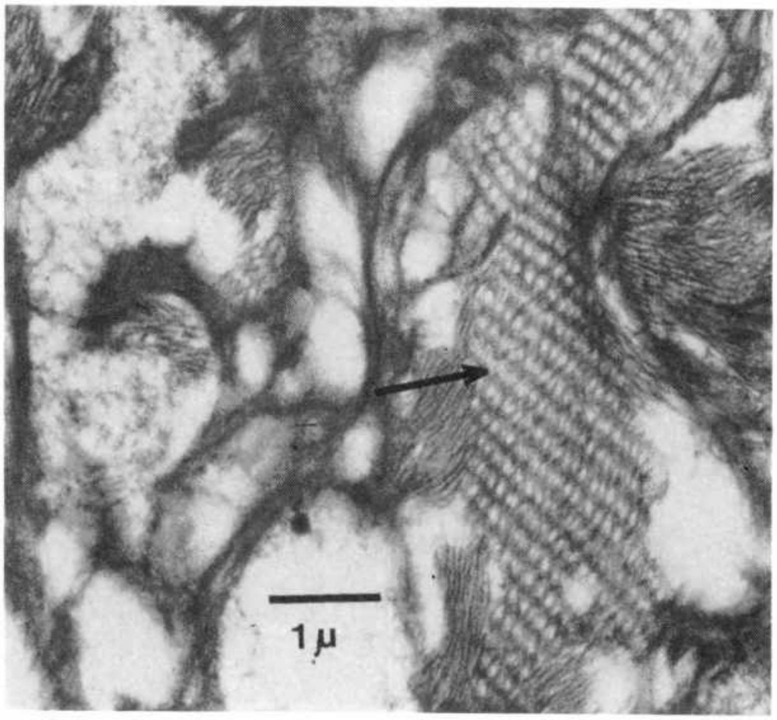

Fig. 5 *Electron micrograph showing Lüse bodies (arrowed) composed of long-spaced collagen. (×15 000.)*

The tumour was therefore classified as a neurilemmoma arising from a nerve sheath.

Discussion

This tumour showed the extensive collagenisation recorded within orbital tumours but in addition had the classical Antoni A areas of palisaded spindled cells, mixed with the more myxoid areas of degeneration, known as Antoni B. The latter areas, with their cystic potential, are said to account for the intermittent waxing and waning in size noticed clinically by some patients. Both neurilemmomas and neurofibromas are derived from a common stem cell, the Schwann cell, and both may be expected to show S-100 positivity. The more universal staining pattern, however, in this tumour was that associated with a neurilemmoma. Fibroblastic tumours do not stain with S-100 and on electron microscopy do not have the prominent basal laminae or interdigitating processes seen in this case. The Luse bodies[7] seen in Fig. 5 consist of aggregates of long-spaced or broad-banded collagen with an axial periodicity of 130 nm. These bodies were originally thought to be pathognomic of neurilemmomas but are now known to occur in other tumours, including basal and squamous carcinomas and in naevoid tumours, also of neural crest origin.[8] Elsewhere in the eye similar collagen is seen in structures such as Descemet's membrane, of neural crest derivation.

From the surgical point of view this case illustrated the potential risk associated with the removal of an apparently superficial tumour from the globe. If the sclera is thin, there is a risk of rupture, and the possibility that a scleral patch graft may be required should be borne in mind.

We are grateful to Professor Roy Weller, of Southampton, for performing the neurofilament staining

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Intravitreal ganciclovir in CMV retinitis: case report

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SUMMARY A case is reported of a 35-year-old male with established acquired immune deficiency syndrome who developed cytomegalovirus retinitis. When intravenous treatment with ganciclovir had to be withdrawn because of toxicity, one eye was treated successfully by intravitreal injections of the drug. After 15 weeks of intravitreal treatment this eye developed endophthalmitis.

A frequent ophthalmological complication of the acquired immune deficiency syndrome (AIDS) is cytomegalovirus (CMV) retinitis.[1-4] Until recently this blinding condition was untreatable. However, the acyclovir analogue ganciclovir given intravenously has been shown to be effective in CMV retinitis,[5] with an 88% response rate.[6] There are disadvantages to its use. Firstly, it is a virostatic agent and maintenance treatment is required.[6-8] Secondly, it is toxic, and neutropenia occurs in up to 38% of patients on maintenance treatment.[8 9] Thirdly, 'breakthrough' disease is encountered on maintenance therapy in up to 50% of patients.[8] We report on a patient who has had intravitreal injections of ganciclovir when systemic treatment had to be abandoned owing to neutropenia.

Case report

A 35-year-old male homosexual with established AIDS presented in March 1987 with painless loss of vision in the left eye of three days' duration. Ocular examination showed a corrected visual acuity of 6/5 right and 6/9 left, with extensive loss of temporal visual field in the left eye. Biomicroscopy revealed flare in the aqueous of the left eye, and on funduscopy there were the typical changes of CMV retinitis involving the nasal retina of the left eye up to and surrounding the optic nerve head. In addition there was a haemorrhagic patch of retinitis just inside the inferior temporal arcade of the right retina 2–3 disc diameters in area (Fig. 1).

The patient was admitted to hospital and started on intravenous ganciclovir 5 mg/kg daily. On admission his white cell count was 1·8×10^9/l, and rectal biopsy showed mild proctitis with CMV inclusion particles. After an initial decline in the vision of the left eye the disease came under control, and maintenance treatment of 5 mg/kg on three days per week was started. During this period his white cell count fell, the dosage of maintenance treatment was halved, but after 12 weeks of treatment his white cell count had fallen to 0·8×10^9/l and intravenous ganciclovir had to be discontinued. His visual acuity at this time was 6/12 right, 6/24, left.

We decided to treat the right eye by intravitreal injections of ganciclovir. Injections of 200 µg ganciclovir in 0·1 ml of normal saline were prepared in a sterile cabinet and passed through a Micropore filter giving a near maximum soluble solution of pH 10·14. After topical anaesthesia with amethocaine 1% drops the injections were made through the inferior pars plana via a 27 gauge needle on a tuberculin syringe. The circulation at the optic nerve head was checked after each injection; we did not find it necessary to perform an anterior paracentesis. Topical chloramphenicol 0·5% drops were given four times a day, on the days preceding and following as well as on the day of each injection. The treatment was given twice weekly for three weeks and weekly thereafter. The injections were generally well tolerated. The retinitis in the right eye showed a good response to this treatment while the retinitis in the left eye showed rapid progression. By the thirteenth week of intravitreal therapy the visual acuity of the untreated left eye was hand movements, that of the right eye remained at 6/12, but funduscopy showed new haemorrhages and exudates extending on both sides of the fovea (Fig. 2).

After 15 weeks of intravitreal treatment (total dose 30 mg) the patient returned to the clinic with a painful, red right eye. He was admitted to hospital for treatment of a right endophthalmitis. A specimen from diagnostic vitreous biopsy grew a mixture of two

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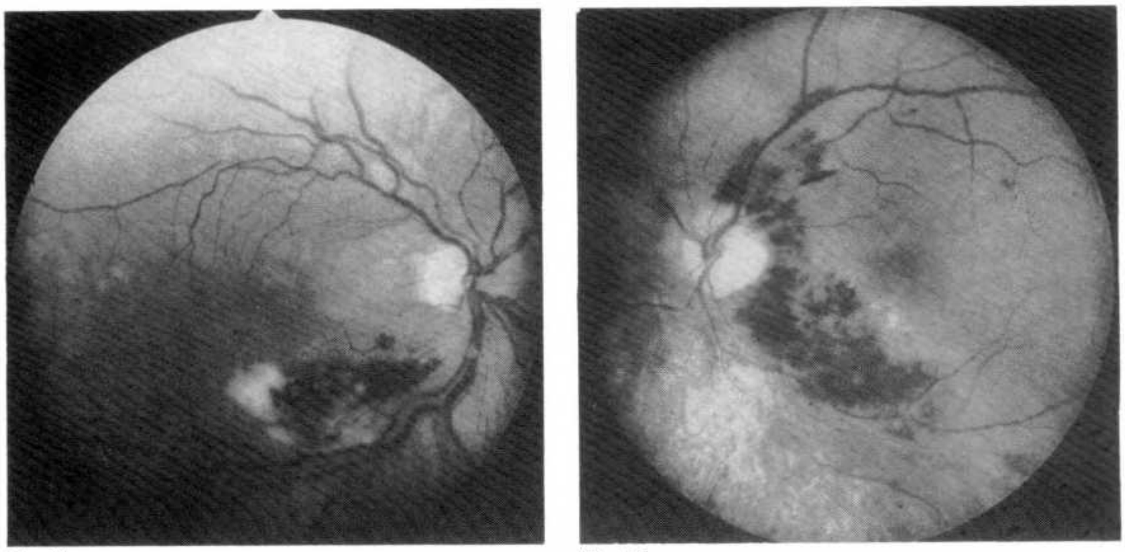
Fig. 1A
Fig. 1B

Fig. 1A, B *Right and left fundi at presentation, showing active retinitis in both eyes.*

coagulase-negative staphylococci, both resistant to chloramphenicol and one also to methicillin. His endophthalmitis responded to treatment, the vision recovering from perception of light to counting fingers. Concurrently he had developed a recurrent pneumocystis pneumonia and died 18 days later. Permission for post-mortem examination was not obtained.

Discussion

In 1985 Pulido *et al.*[10] found no ophthalmoscopic or histological changes on the retina after single-dose injections of ganciclovir into rabbit vitreous. Henry *et al.*[11] have reported the use of this agent via intravitreal injection in one case of CMV retinitis. Using an ID_{50} (dose sufficient to reduce viral replication to

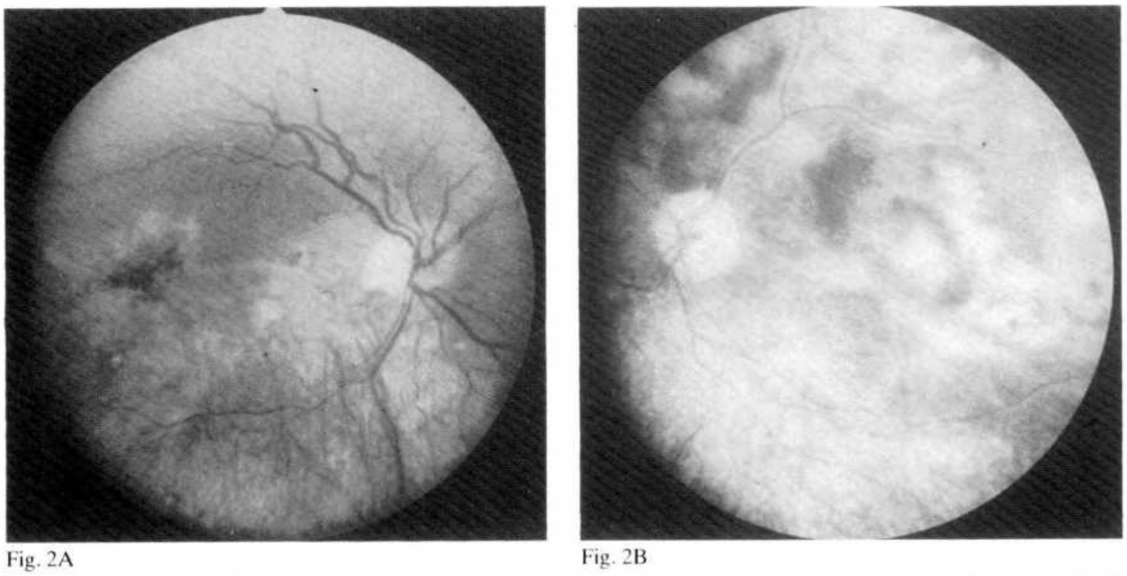
Fig. 2A
Fig. 2B

Fig. 2A, B *Right and left fundi after 14 weeks of intravitreal ganciclovir to the right eye. Note active edge of retinitis on both sides of the right fovea* (A) *and widespread destruction of left retina with secondary optic atrophy* (B).

50%) value of 2·87 μg Henry *et al.*[11] calculated that the intravitreal concentration of the drug remained above this level for approximately 62 hours after a single intravitreal injection of 200 μg. They were able to control the retinitis in their patient with weekly injections. Our case confirms that intravitreal administration of ganciclovir can be used as an alternative route in cases where the use of intravenous therapy is limited by the occurrence of leucopenia. The late recurrence of disease raises the question of whether maintenance treatment of weekly 200 μg is sufficient to control the retinitis adequately. A larger dosage may be desirable, but 200 μg in 0·1 ml is close to the maximum solubility for the drug. Injecting larger volumes intravitreally would certainly require anterior paracentesis to prevent increased intraocular pressure. It remains to be proved that repeated injections of this alkaline agent are not retinotoxic.

This case was complicated by the endophthalmitis, which was always a possibility in this situation. Staphylococci are the commonest cause of endophthalmitis[12,13] and are remarkable for their ability to develop resistance to antibiotics. This makes the choice of prophylactic agents difficult

In conclusion, ganciclovir has been found to be an effective agent when used intravitreally in CMV retinitis. A maintenance dose of 200 μg weekly does not exclude the possibility of breakthrough of the disease. Endophthalmitis is a constant threat when repeated intravitreal injections are given

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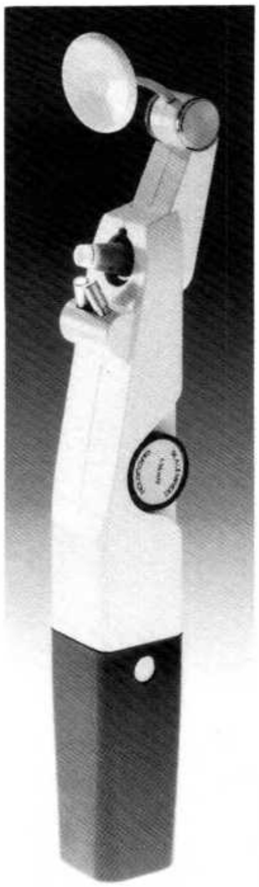

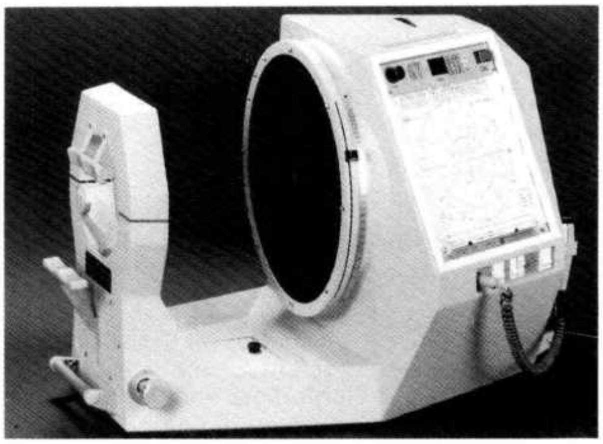

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British Journal of Ophthalmology, 1989, **73**, 385–387

Keratoglobus in the Rubinstein-Taybi syndrome

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From the Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF

SUMMARY The case of a 20-year-old male with the Rubinstein-Taybi syndrome associated with unilateral acute corneal hydrops is presented. The initial findings were of keratoglobus, but after the corneal oedema had settled the cornea sssumed a more conical contour. The relationship between keratoglobus, keratoconus, and acute hydrops is discussed.

Rubinstein-Taybi syndrome is a condition of broad thumbs and toes, facial abnormalities, and mental retardation that was first described in 1963.[1]

We describe a patient with this syndrome who developed unilateral acute corneal hydrops. Corneal ectasia has not been described in association with this syndrome previously. Initially the hydropic cornea was globular in contour, but later, as the oedema settled, the cornea assumed a more conical shape. The relationship between keratoglobus, keratoconus, and acute hydrops is discussed.

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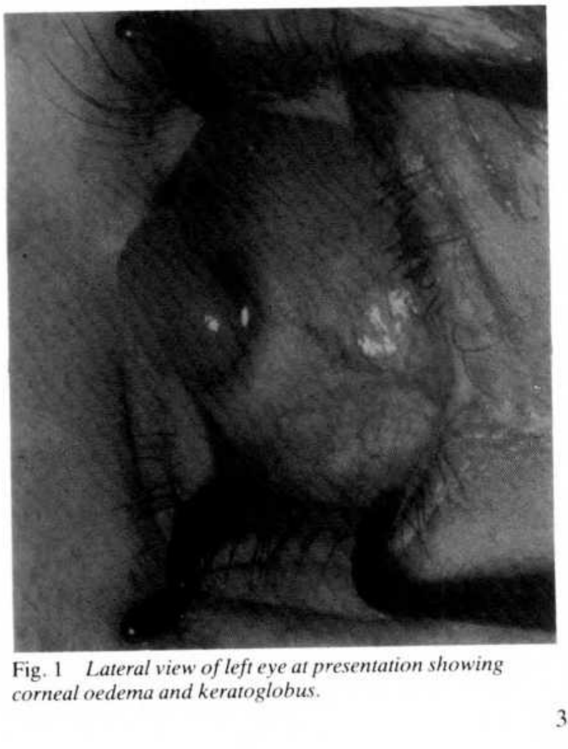

Fig. 1 *Lateral view of left eye at presentation showing corneal oedema and keratoglobus.*

Case report

A 20-year-old male with Rubinstein-Taybi syndrome presented to the Ophthalmology Department of the Royal Hallamshire Hospital, Sheffield, with a painful left eye. Six months previously the patient's father had noted the left cornea to be bulging, and two days before presentation the cornea had become opaque. The patient was in pain, extremely distressed, and very difficult to examine.

The diagnosis of Rubinstein-Taybi syndrome had been made when the patient was 2 years old at the Sheffield Children's Hospital. He was mentally retarded, microcephalic, and had typical features of the syndrome with a beaked nose, hypertelorism,

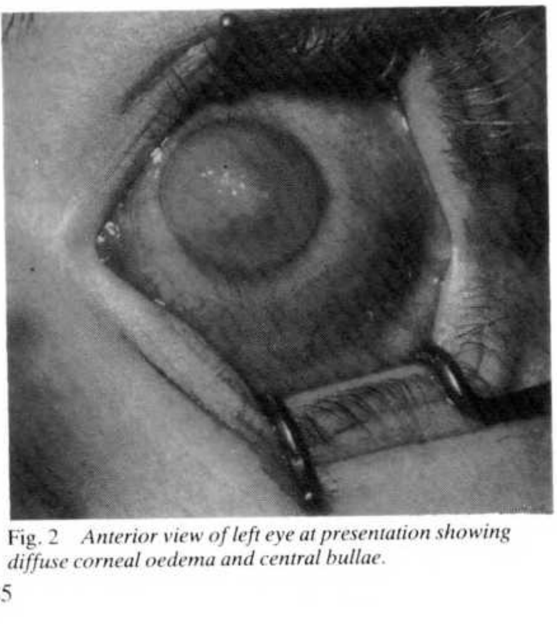

Fig. 2 *Anterior view of left eye at presentation showing diffuse corneal oedema and central bullae.*

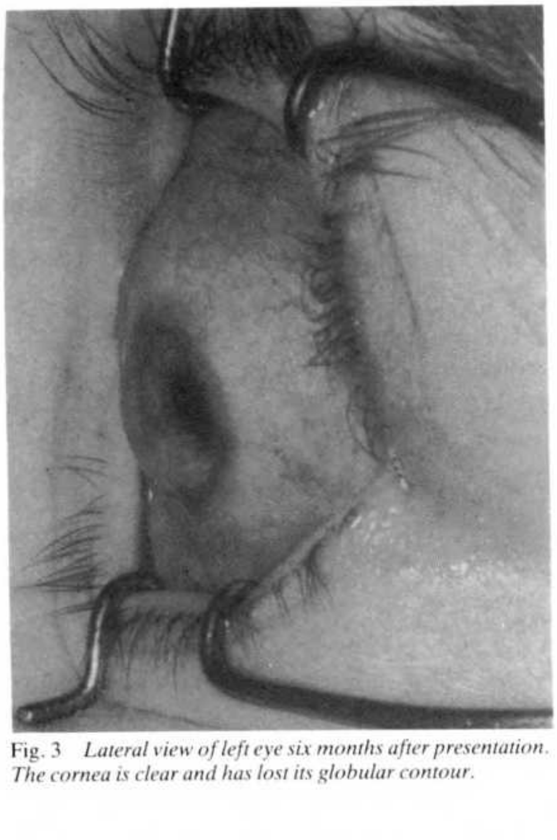

Fig. 3 *Lateral view of left eye six months after presentation. The cornea is clear and has lost its globular contour.*

and broad thumbs and toes. He had a convergent squint and underwent surgery, but no other ocular abnormalities were noted.

Examination under ketamine anaesthesia showed that the left cornea was diffusely bulging and oedematous with a globular contour (Figs. 1, 2). The cornea was thinned apart from the central area, which was irregular and markedly oedematous. No view of the anterior chamber was possible. The intraocular pressure was 19 mmHg and the corneal diameter 11 mm. The right eye showed no evidence of corneal thinning or ectasia.

A diagnosis of unilateral keratoglobus with acute hydrops was made and a subconjunctival injection of 4 mg of betamethasone given. Treatment was symptomatic, with topical prednisolone drops and mydriatics. Over the following four weeks the symptoms settled, and he became less distressed but no more co-operative.

Six months later he was re-examined under ketamine anaesthesia. The left cornea had cleared but was markedly thinned and protruding. The peripheral cornea was vascularised and the central stroma scarred, though the overlying epithelium was intact (Fig. 3). The anterior chamber was quiet and of normal depth. Intraocular pressure was 20 mmHg in both eyes.

Discussion

The syndrome of broad thumbs and toes, facial abnormalities, and mental retardation was described by Rubinstein and Taybi in 1963.[1] They reported on seven children who were severely mentally handicapped, microcephalic, and who had broad thumbs and great toes. Other features since reported include hypotonia and disturbed gait, frequent chest infections, a beaked nose, external ear abnormalities, a high narrow palate, and several skeletal anomalies.[2]

The ocular features of the syndrome have been described.[3] Ptosis, antimongoloid slant of the palpebral fissures, strabismus, refractive error, epicanthal folds, optic atrophy, cataract, coloboma of the iris, and high arching eyebrows were included in the features described by Rubinstein and Taybi in their original report. Roy *et al.*[4] add long lashes and nasolacrimal duct obstruction to this list.

Corneal ectasia is not listed as an association, though one of Rubinstein and Taybi's initial cases was reported as having a corneal scar.[1] The association of keratoconus with Down's syndrome is well known, approximately 5% of these patients being affected.[5] Acute hydrops in Down's syndrome is more common than in other patients with keratoconus[6] and may be associated with eye rubbing. To our knowledge keratoconus has not been reported in association with Rubinstein-Taybi syndrome.

The relationship between keratoglobus and other corneal abnormalities, especially keratoconus, megalocornea, and buphthalmos has been the source of some confusion in the past.[7] However, keratoglobus is now listed as a corneal ectasia, together with keratoconus, pellucid marginal degeneration, and posterior keratoconus.[8]

Keratoglobus is characterised by thinning and protrusion of the entire cornea, which is otherwise of normal size. Corneal thinning is most marked peripherally. Ruptures of Descemet's membrane leading to acute hydrops do occur,[9 10] and the cornea is susceptible to rupture owning to its extreme thinness.[9]

Pouliquen recognises two types of keratoglobus.[11] The first is a rare bilateral condition that is usually congenital, with an autosomal recessive inheritance. It may also occur as part of a syndrome with joint hyperextensibility, deafness, and blue sclerae.[12] The second type of keratoglobus is less common and may be unilateral. It arises in an abnormal cornea, usually in keratoconus, though it has been described with hyperthyroidism.[13] Pouliquen considers this form as severe keratoconus.

As the patient reported here had the appearance of keratoconus after the hydrops had settled, his condition may be classified as the second type of keratoglobus.

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Primary malignant melanoma of the orbit arising in a cellular blue naevus*

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SUMMARY Primary malignant melanoma of the orbit is a rare clinical entity. We report the clinical course and present the light and electron microscopic findings in a case arising in a cellular blue naevus. While most orbital melanomas are associated with a naevus of Ota, there was no clinically visible abnormal pigmentation in our patient. The possible origin of the tumour cell and its ultrastructural features are discussed.

Primary orbital melanomas are extremely rare. Reports are few,[1-8] and in most cases the tumours are associated with oculodermal melanosis (naevus of Ota). We present a case of a very slowly progressing malignant melanoma of the orbit without clinically visible pigmentation. It was a diagnostic problem as well as a problem in terms of treatment and management of the patient. We also discuss our ultrastructural findings with regard to the origin of the tumour cell and the specific features associated with a certain localisation of a melanocyte.[9]

Case report

In May 1980 a 27-year-old male presented at our clinic with slight proptosis of his right eye. No other pathological findings could be detected. When reexamined in December 1980 a right orbital mass was present, indenting the globe inferiorly and nasally. CT scan showed a solid, non-fatty, and moderately vascularised lesion. Because of recently developed pain a biopsy was performed two months later. Histologically this was reported to be a blue naevus whereas the clinical impression was that of a varix. By September 1982 all symptoms had vanished.

In December 1984 the patient complained again of pain and exophthalmus, so another biopsy was done and a 'cyst' was drained. Several experts were consulted on the histology of the specimen There was, however, no uniform opinion on the diagnosis and malignancy of the lesion, opinion ranging from lymphatic tumour to naevus and to malignant melanoma. Clinically it still appeared as a varix. In the meantime the patient had again recovered completely. It was not until February 1987 that severe pain necessitated another biopsy (histology no. 9785). The final diagnosis was now made and the right orbit was exenterated (histology no. 9801). Visual acuity had always remained better than 5/6.

PATHOLOGICAL FINDINGS

Biopsy specimen 9785

On macroscopic examination the specimen consisted of several fragments of soft blood-stained tissue taken from the 'capsule' as well as from the central part of the tumour. They were fixed separately in 2% glutaraldehyde, and a fragment from the capsule was also fixed in formalin. Some tissue fixed in glutaraldehyde was kept for electron microscopy; the remaining fragments were processed for routine light microscopy. Macroscopically there were no specific features.

On light microscopy the specimen taken from the tumour periphery showed a collagenous matrix containing several nests of naevus cells (Fig. 1), some of which were heavily pigmented, whereas others were pale and of rather neuroid appearance. Adjacent to this tissue the histological features were similar to those of the material which was removed from the central part of the tumour. Here the cells were tightly packed without deposition of any extracellular sub-

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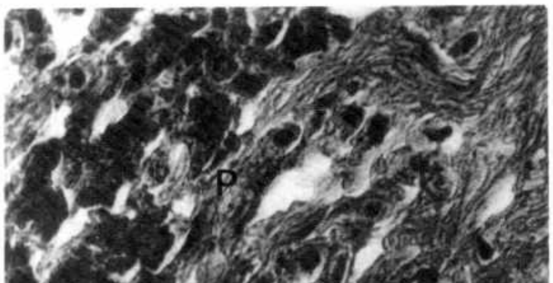

Fig. 1 *Biopsy (9785) taken from the tumour periphery, showing features of a cellular blue naevus. Note heavily pigmented cells* (P) *and lighter cells of neuroid appearance* (N). *Haematoxylin-eosin,* ×*730.*

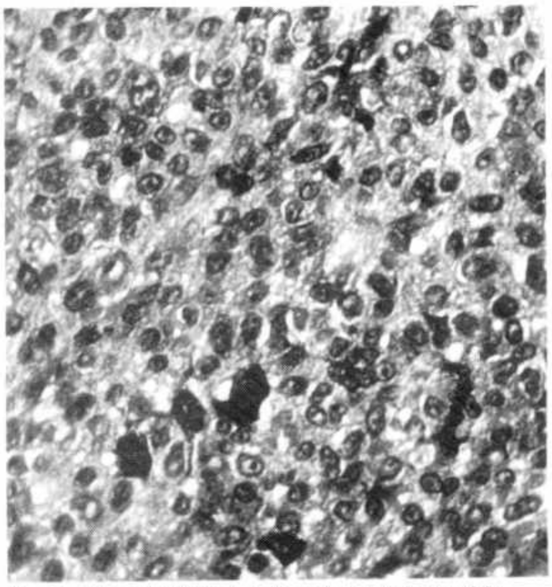

Fig. 2 *Biopsy (9785) taken from the central part of the tumour, showing tightly packed cells with prominent nucleoli. Only a few cells contain pigment, and no extracellular matrix can be identified. Haematoxylin-eosin,* ×*730.*

stances (Fig 2). They were of spindle to epithelioid cell type with prominent nucleoli, and mitotic figures could be seen in a varying degree. There was some cellular pleomorphism and nuclear atypia as well as haemorrhage and necrosis in some areas. Melanin could be detected only with difficulty, even when using the Masson-Fontana stain.

For electron microscopy small blocks of the 'capsule' (7-87) and of tumour tissue (8-87) were dehydrated through graded alcohol and embedded in Araldite. Semithin sections were cut with a Reichert-Jung Ultracut microtome and stained with toluidine blue. Ultrathin sections were cut with the same microtome, stained with uranyl acetate and lead citrate, and visualised with a Zeiss 109 electron microscope.

The light microscopic impression of two populations of naevus cells could be confirmed ultrastructurally (Fig. 3). Embedded in bundles of collagen fibres, one cell type showed dark nuclei with clumped chromatin but no distinct nucleolus and contained numerous melanosomes of different stages and size. The other cell type had a more electron-lucent nucleus and fewer cytoplasmic organelles. Several autophagolysosomal collections of melanin, which are only rarely seen in ordinary naevus cells, were rather conspicuous, and occasionally a basement membrane could be observed.

The melanoma consisted of polyhedral cells lying close together (Fig. 4). Even by electron microscopy no extracellular matrix formation could be seen. Most of the cellular nuclei were deeply indented or showed nuclear pockets; the chromatin was finely dispersed without margination at the nuclear membrane, and large wiry nucleoli were a prominent feature.

The cytoplasm contained numerous mitochondria and endoplasmic reticulum as well as golgi zones and sometimes basal bodies were easily visible (Fig. 5). The rough endoplasmic reticulum often showed a conspicuous whorl formation. In most tumour cells the cytoplasm was of a granular substructure due to free ribosomes, but in some cells cytoplasmic filaments were present (Fig. 6). Premelanosomes were not seen in the sections examined, and hardly any melanin granules or melanophagosomes could be identified (Fig. 5). Occasionally melanosome-like bodies were seen next to a Golgi apparatus. These cells, however, also contained neurosecretory

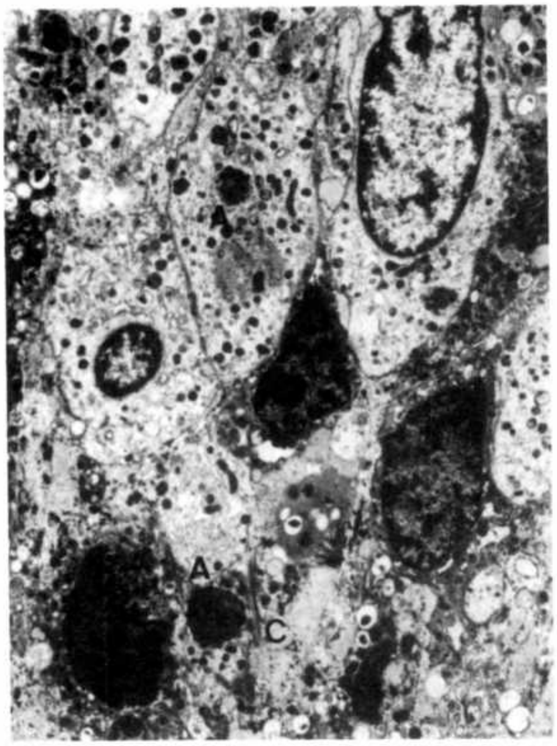

Fig. 3 *Ultrastructural appearance of naevus cells (7-87). Note difference in nuclear chromatin and cytoplasmic density.* A: *autophagolysosomal accumulation of melanin.* C: *collagen fibres. ×4700).*

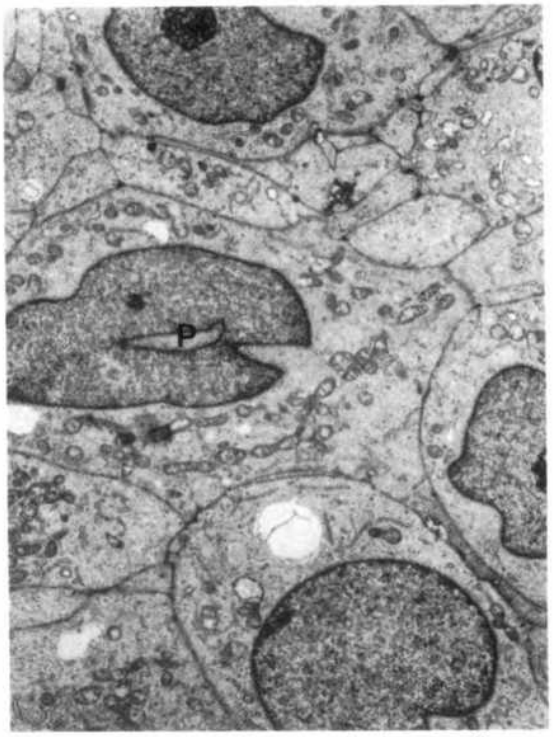

Fig. 4 *Ultrastructural appearance of melanoma cells (8-87). Note prominent nucleoli and nuclear pocket* (P) *and abundant mitochondria. ×4700.*

granules and appeared to be of Schwann cell origin (Fig. 7), though a basement membrane could not be demonstrated.

The individual cell configuration often showed prominent interdigitations and rudimentary elongated cellular processes indicative of abortive dendrite formation. Many desmosome-like junctions were present (Figs. 5, 6), and in addition we found one rather unusual form of cellular connection which might be the ultrastructural appearance of a very late mitotic figure: the cell membrane of two adjacent cells was interrupted for a distance of 0·3 μm, and this gap was traversed by a bundle of intermediate filaments approximately 10 nm in diameter (Fig. 8).

Exenteration specimen 9801
On macroscopic examination the specimen measured 50×46×40 mm with a nodular mass in the posterior inferonasal quadrant (approximately 26×23×18 mm). After fixation in 2% glutaraldehyde an oblique section was taken across the globe and the tumour. The tumour cut surface showed lobulated whitish tissue with only slight pigment dusting at the centre and some foci of heavier pigmentation at the periphery. There were also areas of necrosis, and on the second cut surface there was scar tissue indicating the site of the previous biopsy. No definite capsule was seen. The eye itself appeared unremarkable; in particular there was no evidence of any intraocular tumour. No particular pigmentation within the globe was noted.

The light microscopic appearance of the tumour was similar to that seen in the biopsy specimen. At the periphery there were heavily pigmented naevus cells embedded in a collagenous matrix, whereas the main tumour mass consisted of rather tightly packed cells of spindle or epithelioid type with prominent nucleoli. Even when using the Masson-Fontana stain for melanin hardly any pigmentation could be detected, and mitotic figures were inconspicuous. Only small foci of lymphocytic infiltration were seen. There were, however, large areas of tumour necrosis and degeneration. At the site of the previous biopsies there was some reactionary scar tissue with deposition of iron pigment. No significant pathological changes could be detected in the ocular tissues: there was only marked peripheral microcystoid degenera-

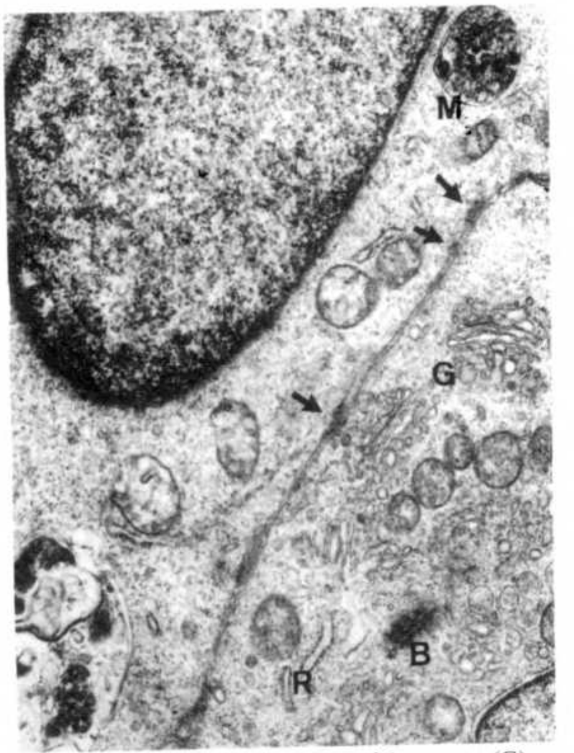

Fig. 5 *Tumour cell with prominent golgi apparatus* (G), *endoplasmic reticulum* (R), *and basal body* (B). *Note melanophagosome* (M) *in adjacent cell and several desmosome-like cell junctions (arrows). ×17 600.*

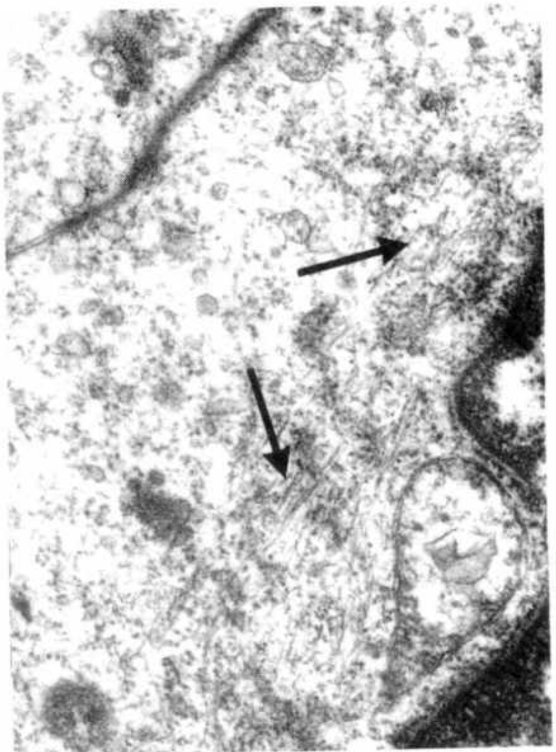

Fig. 6 *Tumour cell with cytoplasmic filaments (arrows). Again, many intercellular junctions are present. ×33 000.*

tion of the retina and an artificial detachment of the choroid in some parts. There was no evidence of uveal hyperpigmentation or intraocular tumour formation, nor was there any indication of scleral invasion by the orbital melanoma.

Owing to inadequate fixation for electron microscopy the quality of the ultrathin sections was rather poor. We therefore concentrate on our ultrastructural findings in the biopsy specimen. Basically, the main morphological features were—as already shown by light microscopy—similar in both specimens.

Discussion

Only few cases of primary malignant melanoma of the orbit have been reported,[1-8] and until now there has not been much information on their clinical behaviour.

Quite often primary orbital melanoma is associated with a naevus of Ota, showing a heavily pigmented skin and/or choroid at the site of the involved orbit.[2 3 5 8] In our patient, however, there was no visible sign of any abnormal pigmentation suggestive of a melanocytic lesion. In addition the clinical (that is intraoperative) impression was much more in favour of a vascular process, since the tissue removed was rather soft, being 'encapsulated' by some firmer tissue. The first biopsy histologically excluded the suspected varix but was reported as showing a benign naevus. This diagnosis was supported by the long-standing history and the lack of any severe symptoms until a further biopsy had to be taken because of painful proptosis seven years after the onset of the disease. By that time there was definite evidence of malignant transformation. It therefore seems of great importance to consider the possibility of malignancy despite a benign clinical course. This is supported by some reports describing orbital melanomas which developed and expanded rather slowly.[1 4 7]

The cellular origin of the orbital melanoma is not clear. Although in our case there was a cellular blue naevus as a predisposing lesion, this only transfers the problem to the origin of the naevus cell. It has been suggested that melanocytes of the optic nerve sheath can proliferate and undergo malignant trans-

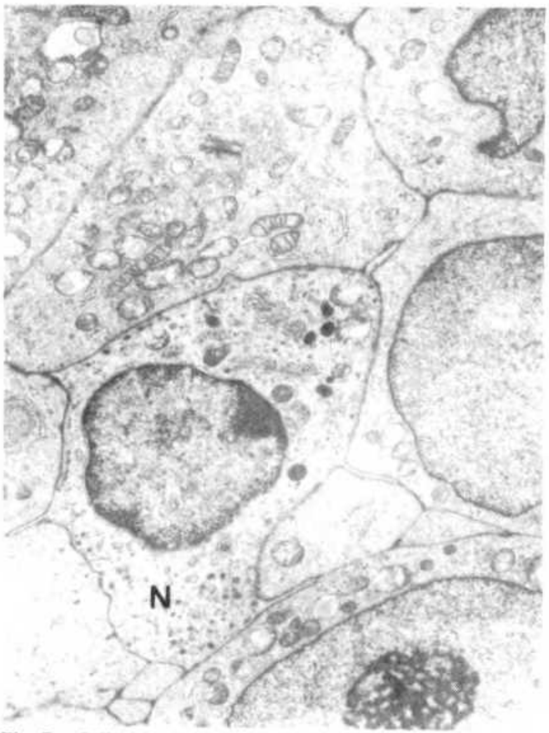

Fig. 7 *Cell within melanoma tissue, containing neurosecretory granules* (N). ×*7600.*

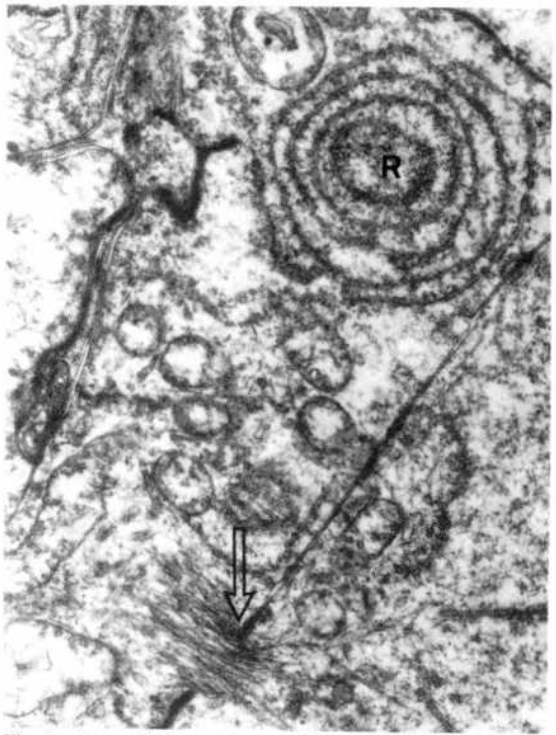

Fig. 8 *Intercellular gap (arrow) bridged by intermediate filaments. Note whorl formation of rough endoplasmic reticulum* (R). ×*18 600).*

formation. This seems unlikely in our patient, since the tumour and in particular the naevus part did not show any connection with the optic nerve and was located in the inferonasal quadrant of the orbit. Indeed there is some evidence of Schwann cell involvement (Fig. 7), which might indicate either a relationship to a peripheral nerve as seen in desmoplastic (neurotropic) melanoma[10,11] or confirm the theory that neoplastic cells in a cellular blue naevus are of Schwann cell origin.[12]

As to the malignant behaviour of a cellular blue naevus, this is well established.[12,13] Presumably there is a similar aetiology for the cellular blue naevus in our patient as for a naevus of Ota—that is, we are dealing with cells which have persisted during development and did not regress as in 'normal' individuals. Thus those hamartomatous cells not responding to growth suppressive factors might already have some genetic defect which makes them more likely to transform into uncontrolled true malignant cells.

On ultrastructural grounds we could not find any particular features specific for 'orbital' malignant melanoma. Since there were so few melanosomes, we do not feel justified in drawing any conclusions from their substructure, as suggested by Jakobiec.[9] Nuclear chromatin, endoplasmic reticulum, and other cytoplasmic organelles were not conclusive in distinguishing a 'benign' naevus cell from a 'malignant' melanoma cell. However, the growth pattern in association with the cytological characteristics, enabled us reliably to establish the diagnosis. One year after the exenteration the patient was well and no metastases had been found.

We thank Mrs Leisin and Mrs Mattes for their technical assistance.

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Corectopia and lipoid proteinosis

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SUMMARY Lipoid proteinosis (Urbach-Wiethe disease) is a rare autosomal recessive disorder associated with deposition of hyalinised material in the skin, mucous membrane, and brain. Corectopia has not been described in this disorder. A case is presented of lipoid proteinosis with bilateral corectopia.

Lipoid proteinosis (Urbach-Wiethe disease) is a rare autosomal recessive genetic disorder characterised by hoarseness beginning in infancy and multiple lesions of mucous membrane and skin.[1] The skin lesions are composed of hyalinised material and appear as clusters of white to yellow papules on the elbows, knees, axillae, perineum, and scrotum. Persons with lipoid proteinosis can present with psychomotor seizures. In some cases intracranial calcification of the hyalinised material has been documented within the hippocampal gyri.[2] Ocular manifestations include papules along the lid margins and retinal drusen. To our knowledge pupillary abnormalities have never been reported in this disorder. We report a case of lipoid proteinosis with bilateral corectopia.

Case report

A 32-year-old man was seen for complaints of bilateral monocular diplopia of two months' duration. The patient had had a persistent hoarse cry from infancy. Psychomotor seizures began at the age of 16 years, and secondary generalised tonic-clonic seizures began at 21. The seizures were successfully controlled with carbamazepine (Tegretol). The patient had several episodes of rage reaction in which he would destroy objects valued by himself and his loved ones. There was no past history of meningoencephalitis, hydrocephalus, stroke, or injury to the head. The patient was born of a full-term uncomplicated pregnancy and delivery. Forceps were not used in the delivery. His parents are first cousins and are in good health. There are no known ocular abnormalities in members of his family, nor are other relatives known to have lipoid proteinosis.

The general physical examination revealed confluent waxy papules on the eyelid margins and face (Figs 1, 2), elbows, knees, and body. The voice was hoarse. The neurological examination gave normal results. Best corrected visual acuity was 20/30 in each eye. Monocular diplopia disappeared when tested with a pinhole. Quantitative automated perimetry was normal. The corneas and gonioscopic examination of the anterior chamber angles were normal.

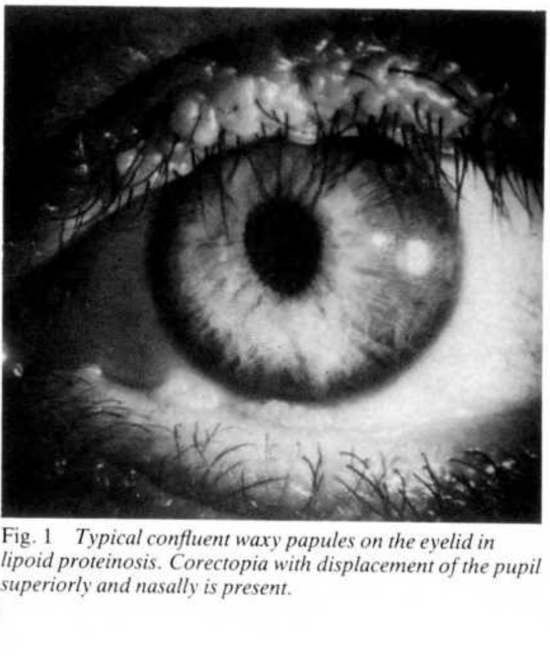

Fig. 1 *Typical confluent waxy papules on the eyelid in lipoid proteinosis. Corectopia with displacement of the pupil superiorly and nasally is present.*

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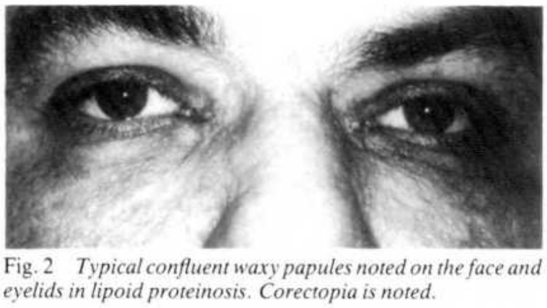

Fig. 2 *Typical confluent waxy papules noted on the face and eyelids in lipoid proteinosis. Corectopia is noted.*

Bilateral nuclear lens opacifications were noted. There was no evidence of posterior synechiae or lens dislocation. The pupils were oval and displaced upwards and nasally (Fig. 1). (Similar corectopia was recorded at 9 months old). The irides were otherwise normal. Pupillary reactions were brisk to light and near stimulation. There was no iris sector palsy or atrophy. No afferent pupillary defect was present. Ocular motility and funduscopic examination were normal. Retinal drusen were not apparent on ophthalmoscopic examination.

A computed tomographic scan, magnetic resonance imaging, and cerebrospinal fluid analysis were normal. Electroencephalography showed bitemporal seizure foci. Skin biopsy had findings characteristic of lipoid proteinosis (Figs 3, 4).

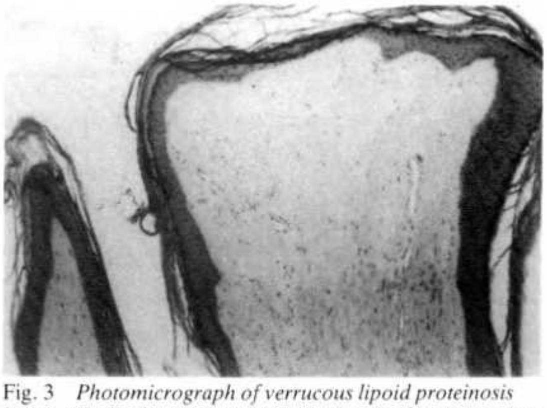

Fig. 3 *Photomicrograph of verrucous lipoid proteinosis lesion. The hyaline material deposited in the dermis consists of homogeneous bundles staining pale pink with haematoxylin and eosin. ×17.*

Discussion

Our patient's clinical history and the findings from the physical examination were suggestive of lipoid proteinosis, with skin biopsy confirming the diagnosis. Histological studies of the dermis in lipoid proteinosis usually show diffuse deposits of amorphous hyalinised material composed in part of neutral mucopolysaccharides[3] round blood vessels.

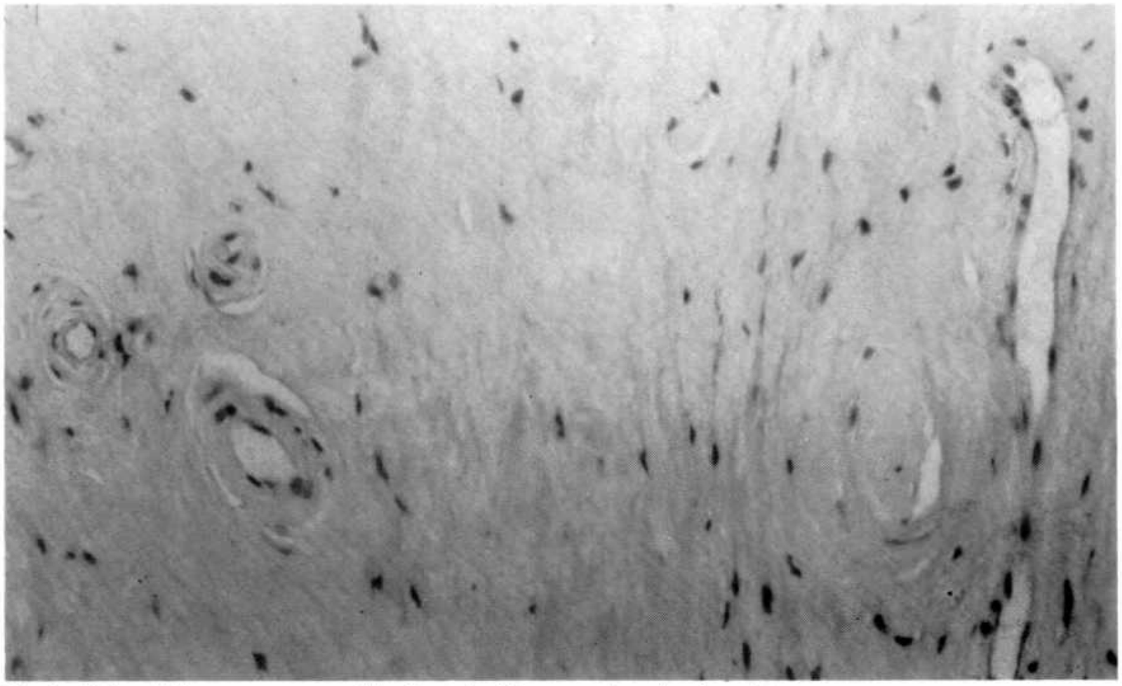

Fig. 4 *'Onion skin' appearance round blood vessels. (Haematoxylin and eosin, ×100.)*

There may be an associated increased number of fibroblasts in the dermis. Lipid deposits are not a notable feature of this disease.

Corectopia had been present in our patient at least since the age of 9-months. It has been shown pathologically to occur in patients with significant rostral midbrain injury, possibly due to partial destruction of the parasympathetic pupillary fibres.[4,5] Our patient did not have a history of severe injury to the head. In addition the seizure disorder began several years after the corectopia was noted. However, hyalinisation of the hippocampal gyri of the temporal lobe has been observed histopathologically in cases of lipoid proteinosis with temporal lobe seizure disorder.[2] Indeed, our patient had bitemporal seizure foci. Although the corectopia may be a consequence of consanguinity, it is conceivable that the hyalinised material noted on skin biopsy was also present in the rostral midbrain, accounting for the corectopia. Although to our knowledge this is the first reported case of pupillary abnormality associated with lipoid proteinosis, this disorder should be added to the differential diagnosis of corectopia.

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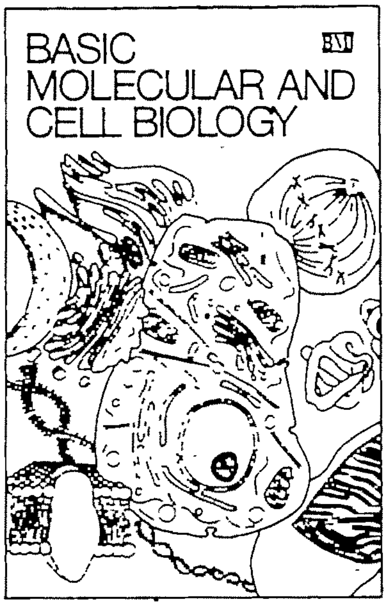

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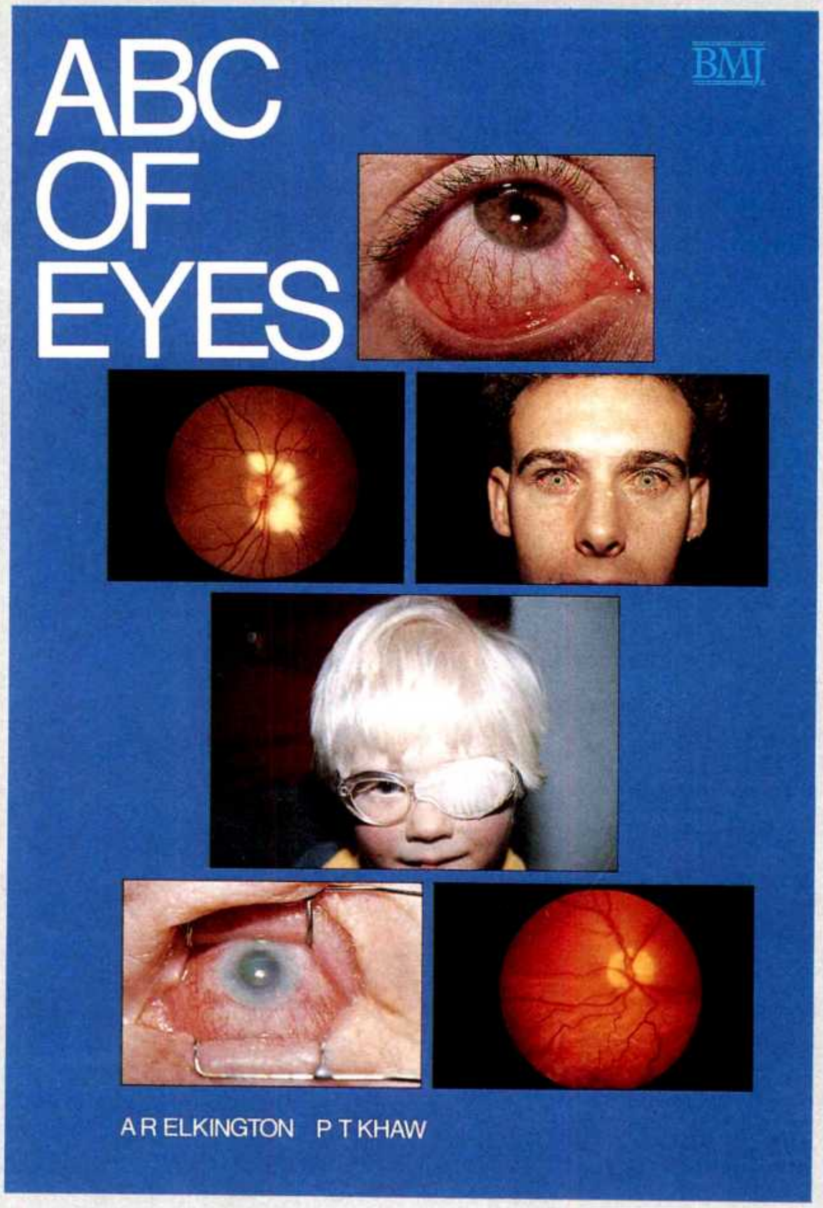

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Amphotericin B induced ocular toxicity in cryptococcal meningitis

PHILIP K T LI AND KAR NENG LAI

From the Department of Medicine, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong

SUMMARY We report a case of acute visual loss after a test dose (1 mg) of intravenous amphotericin B administered to a patient with systemic lupus erythematosus and with cryptococcal meningitis. Her visual acuity was normal prior to the injection of amphotericin B. The meningitis subsequently responded to miconazole and flucytosine treatment. Our findings suggest that amphotericin B should be withheld in the treatment of cryptococcal meningitis if disease of the optic nerve is strongly suspected.

Amphotericin B has been used as a first-line treatment in cryptococcal meningitis.[1] We report a case of acute visual loss after a test dose (1 mg) of intravenous amphotericin B administered to a patient with systemic lupus erythematosus and cryptococcal meningitis. We believe that this is the first report of an intravenous test dose of amphotericin B leading to ocular toxicity in cryptococcal meningitis.

CASE REPORT

A 26-year-old Chinese woman was first diagnosed as suffering from systemic lupus erythematosus with diffuse proliferative glomerulonephritis in 1984. She was maintained on low-dose prednisolone (5 mg/day) and azathioprine (125 mg/day).

She presented to the medical clinic in September 1987 with a four-week history of low grade fever and headache. The clinical examination showed absence of neck rigidity with no localising sign. The appearances on funduscopic examination and visual acuity were normal. Her white cell count was 11×10^9/l and the erythrocyte sedimentation rate was 94 mm in the first hour. Her renal and liver function tests and C3 and C4 levels were normal. Plasma C-reactive protein was 20 mg/l (normal range 0–9·9 mg/l), and the antinuclear antibodies titre was 1:80. Urine and blood cultures were negative. A computerised tomography of the brain did not show any lesion.

A lumbar puncture was subsequently performed because of persistent headache and fever. The cerebrospinal fluid was clear, with a pressure of 30 cm H_2O. Microscopic examination showed white cells (30×10^6/l with 100% polymorphs) and no red cell. The protein and glucose concentrations in the cerebrospinal fluid were 0·4 g/l and 2·8 mmol/l respectively (simultaneous blood sugar 5·8 mmol/l). *Cryptococcus neoformans* was identified with Indian ink stain and later isolated on culture. Bacterial and viral cultures were negative in the cerebrospinal fluid.

The patient was prescribed amphotericin B and flucytosine. A test dose of 1 mg amphotericin B in 20 ml 5% dextrose solution was administered intravenously over 20 minutes. She developed fever, chills, and a rigor after receiving the test dose, so amphotericin B was withheld. Ten hours later the patient complained of bilateral visual impairment. Her visual acuity was reduced to light perception at 60 cm for the right eye and 30 cm for the left eye. Her fundi looked normal, with no papilloedema or optic atrophy. The intraocular pressure was normal. Her visual acuity deteriorated rapidly. The visual evoked potentials of both eyes were unrecordable three days later, and she was totally blind.

Four days later she developed ophthalmoplegia, with failure of abduction of both eyes and impaired upward and downward gaze of the left eye. A repeated computerised tomography of the brain 10 days later did not show any lesion. Intravenous miconazole 600 mg thrice daily and oral flucytosine 1·5 g four times daily were given for a total duration of 10 weeks. Repeated lumbar puncture performed after six and eight weeks' therapy showed no pleocytosis or cryptococcus, and the cultures were negative.

Her ophthalmoplegia subsided five weeks after treatment. The visual failure persisted, with no light perception and loss of light reflexes bilaterally. Bilateral optic atrophy developed 10 weeks after the administration of amphotericin B.

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Discussion

Patients with systemic lupus erythematosus on immunosuppressive therapy are more susceptible than usual to cryptococcal infection. Cryptococcal meningitis may cause progressive visual disturbances such as decreased visual acuity, papilloedema, increased blind spot, optic atrophy, and extraocular muscle paresis[2] Acute blindness with normal funduscopic appearance has not previously been recognised in cryptococcal meningitis. Marked visual loss shortly after intrathecal injection of amphotericin B has been previously reported in two patients with cryptococcal meningitis.[2] Adhesive arachnoiditis or toxic neuritis has been suggested as a possible cause.[2] Our patient, whose vision was previously normal, received an intravenous test dose of amphotericin B and developed acute bilateral blindness within 24 hours. Blurring of vision is a well recognised but uncommon complication of intravenous amphotericin B, but acute blindness has never been reported.[3] We cannot prove that the amphotericin B was the culprit, but a possible idiosyncratic reaction of optic nerves towards the drug is highly likely in view of the temporal relation between the acute onset of blindness and the administration of the test dose. *Cryptococcus neoformans* may rarely invade the optic nerve,[2,4] and whether this would predispose the optic nerve to further injury by the amphotericin B remains speculative.

Amphotericin B has potential renal and neurological toxicity. Since such a low testing dose could cause acute blindness in patients with cryptococcal meningitis, extreme caution should be exercised in administering it to these patients We suggest that it should not be used as a first-line drug in patients with possible optic nerve involvement. Miconazole has been used successfully in treating cryptococcal meningitis.[5,6] Our patient also showed a good clinical and laboratory response to the combination therapy of intravenous miconazole and oral flucytosine. Our findings suggest that miconazole and flucytosine should be considered as the initial treatment in cryptococcal meningitis in preference to amphotericin B if optic nerve pathology is strongly suspected.

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Correspondence

Conjunctival epithelial cells infected with *Chlamydia trachomatis* express HLA-DR antigens

SIR, The major histocompatibility complex (MHC) class II products or HLA-DR antigens are cell surface glycoproteins concerned with antigen presentation and the elicitation of T lymphocyte-dependent immune responses. The class II products are predominantly expressed on immune competent cells such as B lymphocytes, activated T lymphocytes, macrophages, and Langerhans cells.[1] In addition a variety of epithelial cell types are now known to express HLA-DR antigens.[2]

In an immunopathological study of trachomatous conjunctivitis we recently observed that the superficial conjunctival epithelial cell layers express HLA-DR antigens.[3] In order to investigate in detail the topographical relationship between the distribution pattern of HLA-DR antigens on the one hand, and the presence of chlamydial antigens on the other, we performed a double staining technique. HLA-DR antigens were demonstrated with a three-step indirect immunoperoxidase procedure using TAL-1B$_5$ monoclonal antibody,[4] and chlamydial antigens were subsequently visualised in the same sections with fluorescein labelled monoclonal antibodies (BioMerieux, France). Chlamydial antigens were found in variable numbers of superficial epithelial cells, which constantly coexpressed HLA-DR antigens (Fig. 1).

Coexpression of infectious and HLA-DR antigens has previously been reported in human hepatitis[5] and in infections by murine hepatitis[6] and visna-maedi viruses.[7]

The mechanism by which the conjunctival epithelial cells are induced to synthesise these antigens is as yet unclear. Interferon-gamma, released by activated T lymphocytes in the epithelium, may be responsible, since this lymphokine has been shown to induce HLA-DR synthesis and expression in a variety of epithelial cells in vitro.[8,9] Alternatively, and by analogy with the murine hepatitis virus,[6] the chlamydial agent itself could play a causative role.

HLA-DR expression by the conjunctival epithelial cells may render these cells capable of acting as antigen-presenting cells for T lymphocytes, thereby enhancing the immune response and possibly inducing an autoimmune reaction.[10] Alternatively, expression of HLA-DR antigens may render the infected epithelial cells susceptible to

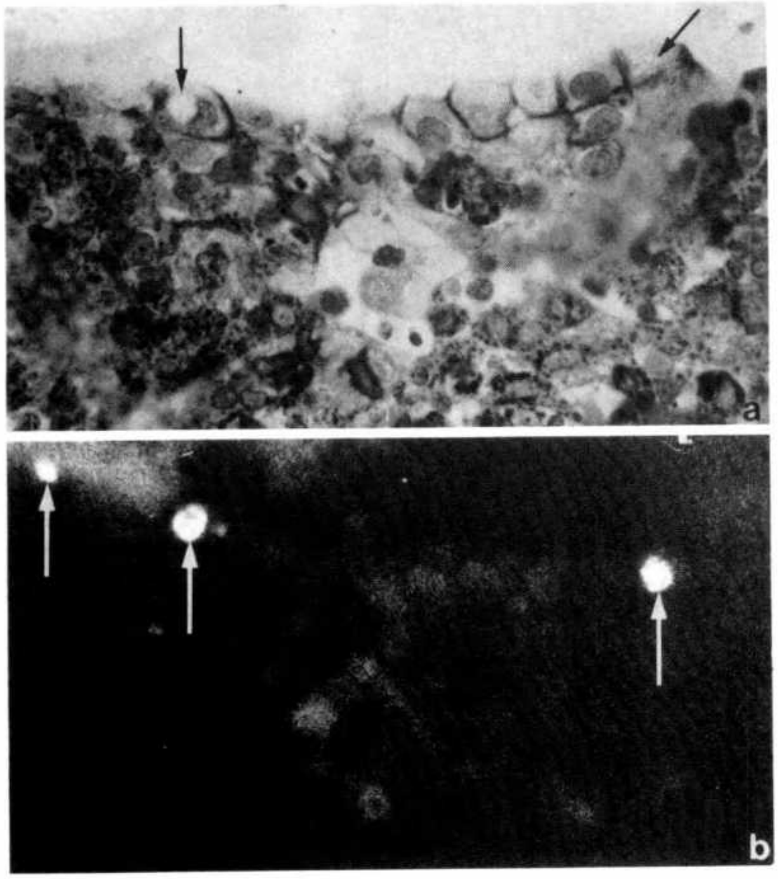

Fig. 1a: *TAL-1B$_5$ staining in trachomatous conjunctivitis. Many epithelial cells in the superficial layer are HLA-DR$^+$. Some of them contain Halberstaedter-Prowazek inclusion bodies seen as pale vacuoles (arrows).* b: *The same section, stained for chalmydial antigens, shows three brightly fluorescing inclusions, indicated with arrows, in the HLA-DR$^+$ epithelial cells. Faint fluorescence of the surrounding structures is due to the counterstaining. (Conjunctival specimen stained with a three-step indirect immunoperoxidase procedure for monoclonal antibody TAL-1B$_5$, and* (b) *subsequently incubated with fluorescein labelled antichlamydial monoclonal antibodies ×480.)*

immunological attack by HLA-DR-restricted cytotoxic T cells.[11]

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Notes

Research grants

The *David Cole travel fellowship*, instituted by Merck Sharp and Dohme in memory of Professor David Cole, will assist a visit to a hospital or research centre during the academic year starting 1 October 1989. The award will be equivalent to £2000. The purpose of the award is to enable the successful applicant to gain experience and knowledge in pursuit of a specific project related to glaucoma.

The Glaucoma Group Research grant, sponsored by International Glaucoma Association, will be available for a research project clinically orientated to glaucoma for 1989. The award will be equivalent to £2500. The grant may be used towards salary or project expenses or for buying equipment

Both these awards are available to medical graduates and non medical scientists resident in the United Kingdom or Republic of Ireland. They may be held concurrently with other awards. Further details and application forms from Dr S Nagasubramanian, Secretary Glaucoma Group, Glaucoma Unit, Moorfields Eye Hospital, City Road, London EC1V 2PD. The closing date for applications is 15 June 1989. The successful candidate will be informed by August 1989.

Association for Eye Research

The thirtieth meeting of the AER will be held in La Grande Motte, near Montpellier, France, on 3–7 October 1989. Further information from the Programme Secretary, Dr John Tiffany, Nuffield Laboratory of Ophthalmology, Walton Street, Oxford OX2 6AW. The deadline for abstracts is 31 May 1989. All proceedings will be in English. The AER Publication Award will be made at this meeting for the best paper in any language, by either members or non-members of AER, published in the 12 months preceding the meeting Eligible authors must be under the age of 35. In the case of multiauthored papers the award will be made to the main author, and the entry must be accompanied by a statement signed by each author, indicating who this is. The work described must relate to the eye and be original or based on a previously evolved technique or method. (If the paper is not in English, it must be accompanied by a translation of captions, results, and conclusions in sufficient detail to permit assessment.) Nominations (eight reprints or eight copies of the manuscript accepted for publication) must be made through a member of the AER to the General Secretary Professor Martin Reim, Abtlg. Augenheilkunde, Med. Fakultat der RWTH Aachen, Klinikum, Pauwelsstrasse, D-5100 Aachen, West Germany, not later than 1 July 1989.

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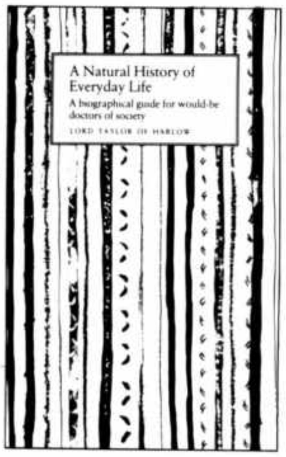

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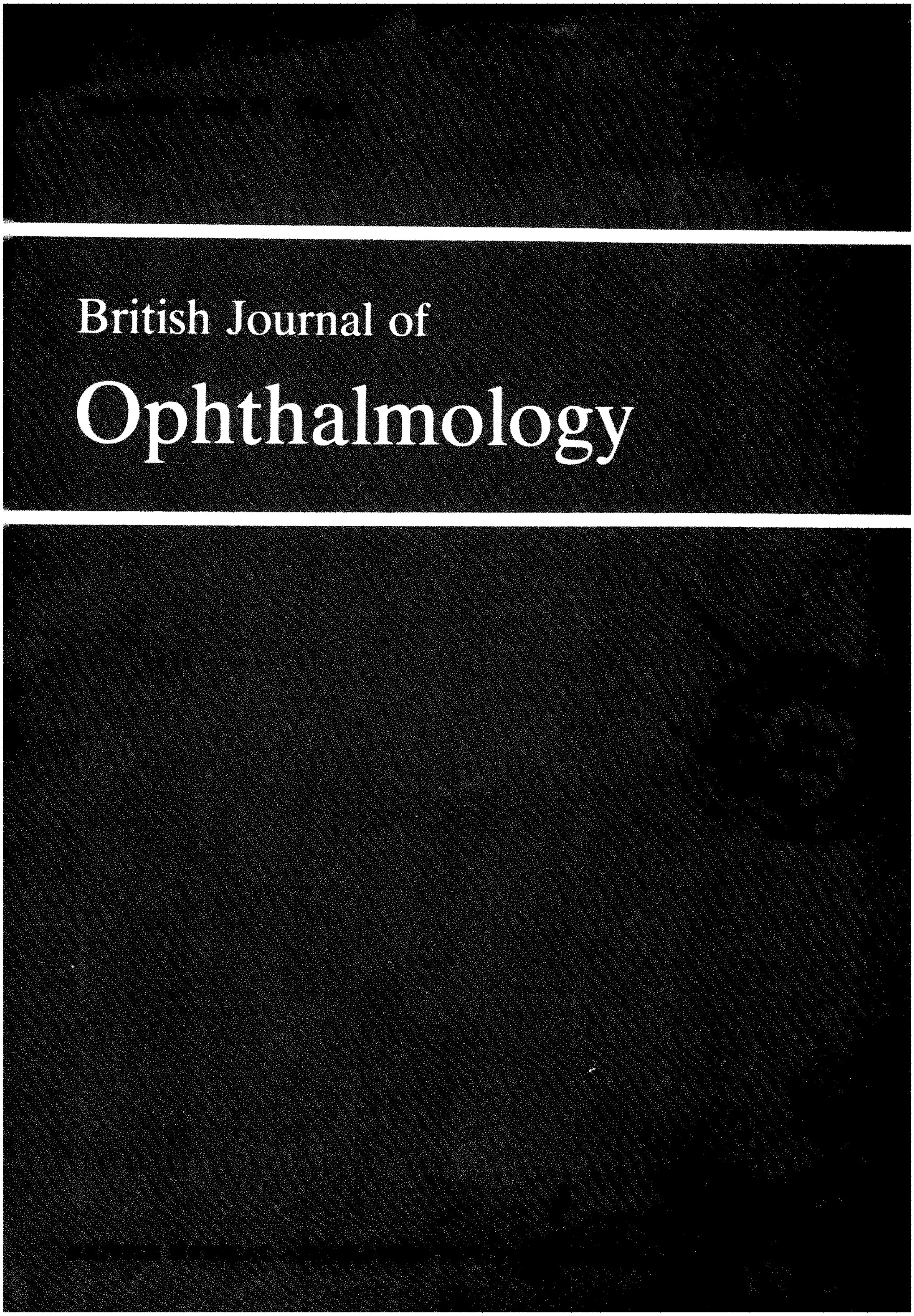

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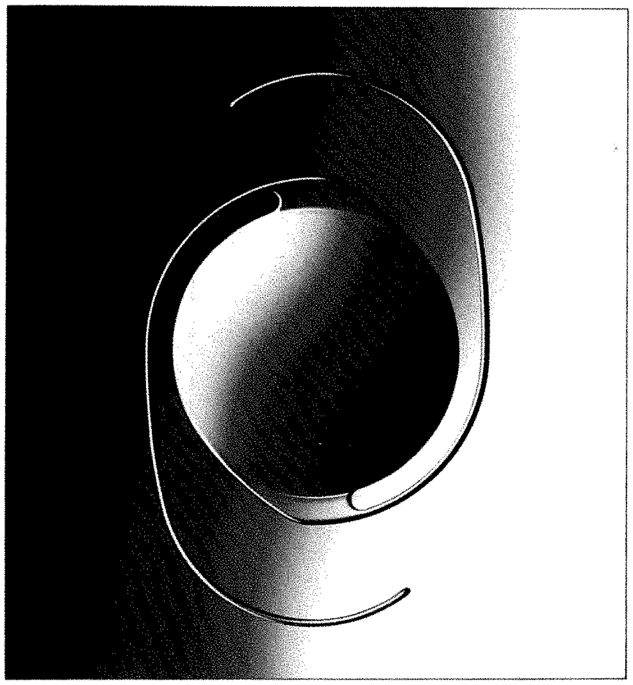

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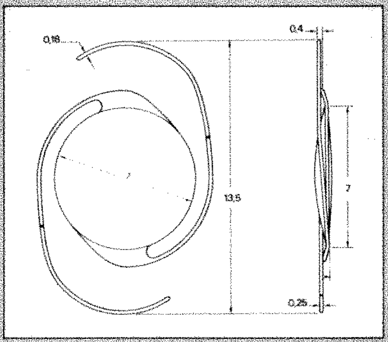

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Bronchial asthma, history of bronchial asthma, severe chronic obstructive pulmonary disease. Sinus bradycardia, second- and third-degree AV block, overt cardiac failure, cardiogenic shock. Hypersensitivity.

PRECAUTIONS

'Timoptol' may cause side effects of systemic beta-blockade.

Cardiac failure should be adequately controlled before prescribing. History of severe cardiac disease requires monitoring for cardiac failure and checking of pulse rates. Respiratory and cardiac reactions (including death) have been reported.

Patients receiving a beta-blocker orally and 'Timoptol' may experience an additive effect on IOP or on known systemic effects of beta-blockade.

Rashes and/or dry eyes have been reported with beta-blockers. Reported incidence is small, and most cases clear on withdrawal. If seen, beta-blockers should be withdrawn gradually.

Do not use in patients with soft contact lenses. Mydriasis resulting from use of 'Timoptol' with adrenaline reported occasionally. Potentially, hypotension and/or marked bradycardia may result from addition of 'Timoptol' to a calcium antagonist, rauwolfia alkaloid or beta-blocker.

Children: Not recommended. Data not available for use in children.

Nursing: Mother should either stop nursing or stop 'Timoptol'.

Pregnancy: Not studied; weigh benefit against possible hazards.

SIDE EFFECTS

Ocular irritation, including conjunctivitis, blepharitis, keratitis, blepharoptosis, and decreased corneal sensitivity. Visual disturbances, including refractory changes (due sometimes to withdrawal of miotics), diplopia, and ptosis.

Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebrovascular accident, cerebral ischaemia, congestive heart failure, palpitation, cardiac arrest.

Bronchospasm (predominantly with pre-existing bronchospastic disease), respiratory failure, dyspnoea.

Headache, asthenia, nausea, dizziness, depression.

Hypersensitivity, rash, and urticaria.

Reactions with an unestablished relationship are ACMO, dry mouth, anorexia, dyspepsia, nausea, dizziness, CNS effects (e.g. fatigue, behavioural changes and other psychic disturbances), hypertension, and retroperitoneal fibrosis.

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Issued July 1988.

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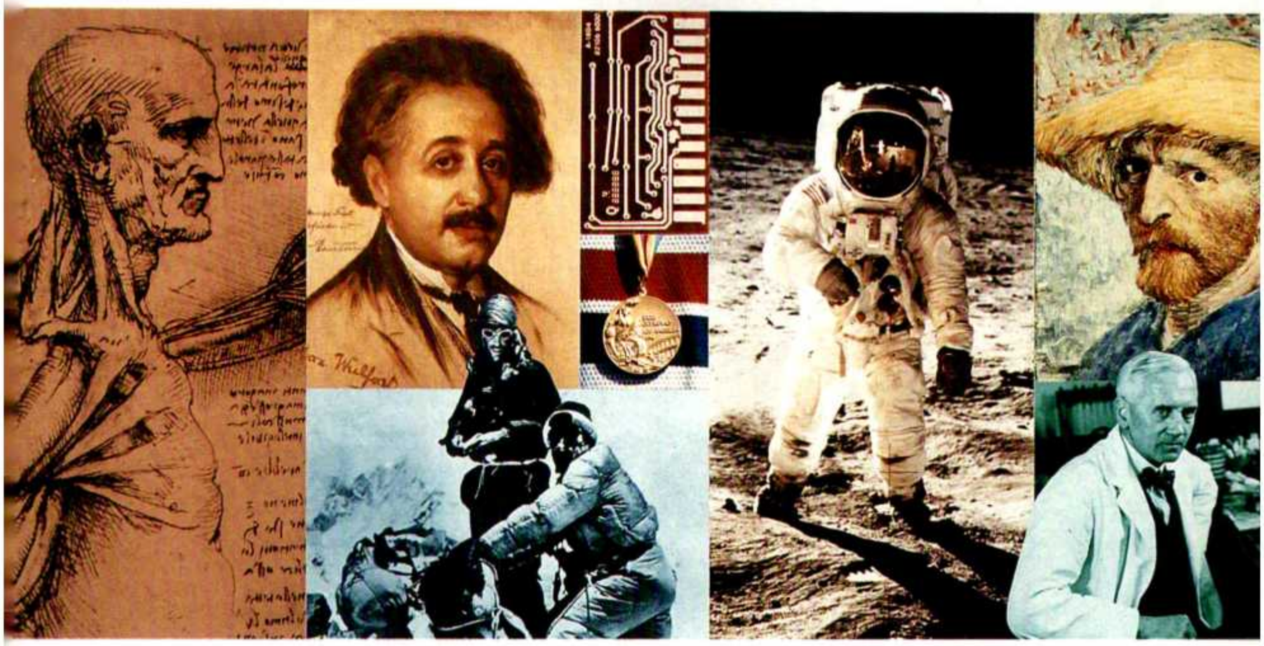

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British Journal of Ophthalmology, 1989, **73,** 401

Editorial: Endophthalmitis following cataract extraction

Endophthalmitis following cataract extraction varies in reported incidence from a minimum of around 0·1%[1] to 0·66%.[2] There is some doubt about the benefit of preoperative antibiotics but probably a consensus in favour of using them. One author even resorted to intravenous chloramphenicol,[3] but since only 520 cases were studied only 0·5 cases of endophthalmitis would have been expected, throwing doubt on the author's claim of success.

Attempts have been made to single out patients most at risk, formerly by conjunctival culture and even by culturing the intracapsularly removed lens,[4] but since many of the infections have occurred in the face of sterile cultures, and others have been due to what are normally regarded as harmless commensals,[5,6] it seems that preoperative cultures have little to offer.

Reports have recently been published suggesting that endophthalmitis behaves somewhat differently when an intraocular lens (IOL) has been used. Infection by organisms normally thought to be of low virulence such as *Propionibacterium acnes* have been implicated,[7] and the infection has pursued a peculiar clinical course, characterised by apparent complete cure followed by repeated severe relapses. I have just such a case at the moment which has remitted completely three times while on metronidazole and Maxitrol (neomycin, polymyxin B, dexamethasone). It is quiescent at the moment, but I am waiting with trepidation for the fourth attack.

As pointed out in the article in this issue by Griffiths, Elliot and McTaggart organisms are known to adhere to implanted foreign material, including heart valves and other indwelling devices. It has also been pointed out[8] that in cataract cases *Propionibacterium acnes* endophthalmitis has been reported only in patients with an IOL. The present paper by Griffiths and colleagues demonstrates elegantly how staphylococci can adhere like limpets to IOLs and furthermore somewhat alarmingly thereby increase their resistance to antibiotics.

The authors put a brave face on it, suggesting certain measures which may help to minimise the dangers, but it is clear that there is a problem here which will not just go away. No one, as far as I am aware, has shown that there is a genuine increased incidence of endophthalmitis due to the increased use of IOLs or whether the incidence is the same but the clinical behaviour different. One's clinical impression is certainly not of an obvious increase in postoperative endophthalmitis, but of course clinical impressions can be misleading. However, one certainly hopes that in this case it is correct.

REDMOND J H SMITH

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British Journal of Ophthalmology, 1989, **73**, 402–406

Adherence of *Staphylococcus epidermidis* to intraocular lenses

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SUMMARY We have demonstrated, with an in vitro model, that *Staphylococcus epidermidis* is able to colonise intraocular lenses. Adherent organisms were quantitated by light microscopy, scanning electron microscopy, and viable counting. Bacterial adherence was associated with production of a polysaccharide glycocalyx. Organisms which were attached to the lenses were resistant to apparently bactericidal concentrations of antibiotics, as determined by conventional testing. We speculate on the role of colonisation in the pathogenesis of endophthalmitis.

Staphylococcus epidermidis is now recognised as the commonest cause of endophthalmitis.[1] This organism is normally considered to be of low pathogenicity, yet its frequency as a cause of endophthalmitis, as well as its occasional late presentation several months after surgery, requires explanation.

The commonest cause of infection of joint replacements and other prostheses, such as indwelling intravenous cannulae, is also *Staph. epidermidis*. This has been related to the organism's ability to adhere to plastic surfaces.[2] There is evidence that this property is associated with the production of a polysaccharide glycocalyx,[3] which acts like a glue preventing mechanical removal. Furthermore 'slime' production confers resistance to bactericidal concentrations of antibiotics when the organisms are adherent to a smooth surface.[4,5]

Intraocular lenses may play a part in the pathogenesis of intraocular infections following cataract surgery. This proposition is supported by recent animal experiments which have shown that when *Propionibacterium acnes* was introduced into the anterior chamber at the conclusion of cataract surgery the presence of an intraocular lens made the eye more susceptible to infection.[6] The resultant infection was also more intense and prolonged than intraocular infections in the absence of artificial lenses.

Bacterial adherence on to surfaces can be divided into two stages. The first stage involves reversible attraction due to electrostatic and Van der Waals forces, and hydrophobic bonding. The second stage involves slime production leading to irreversible adherence. Stage 1 adherence has been demonstrated by Vafidis *et al.*[7] who wiped intraocular lenses round the wound site at the time of surgery and subsequently placed them in nutrient broth. In 26% of cases *Staph. epidermidis* grew in the broth. The lenses were not examined under the microscope after incubation in broth, so this figure is a measure of reversibly adherent organisms.

The present study was designed to determine whether or not stage 2 adherence to intraocular lenses occurs, resulting in firmly attached bacteria. An in-vitro model was developed and bacterial adherence was quantified by light microscopy, scanning electron microscopy, and estimation of viable counts.

Materials and methods

Two clinical isolates of *Staph. epidermidis* were used, namely, E004, a slime producer, and E001, a non-slime producer. An isolated colony of the test organism was taken from a nutrient agar plate and inoculated into 100 ml of brain heart infusion broth (Sigma Laboratories), which was incubated at 37°C for 16 hours. 50 ml of the culture was added to 100 ml of fresh brain heart infusion broth, and the culture was used for the experiments described below.

Three different types of lens were used—closed-loop anterior chamber lenses, and Rayner posterior chamber lenses style 850b and 869.

Lenses were suspended in the bacterial cultures by

Correspondence to Mr P G Griffiths.

fine sterile wire threaded through the dialling holes or haptics. The lenses were then incubated at 37°C for variable periods of time as outlined below. The same type of lens was used for each experiment, so that the results were not biased by differential adherence to different lens surfaces. After all the experiments were completed a sample of the broth culture was subcultured on to nutrient agar to confirm purity.

Lenses were prepared for light microscopy by fixation in 3% glutaraldehyde in 0·1 M sodium cacodylate buffer for two minutes, stained with methylene blue for five minutes, and washed by gentle agitation in three changes of distilled water in a 150 ml beaker before being allowed to dry in air at 20°C. The lenses were prepared for scanning electron microscopy by fixation in the 3% glutaraldehyde cacodylate buffer for two hours, followed by dehydration through ethyl alcohol of increasing concentrations (50%, 75%, 90%, 95%, and 100%) for 10 minutes. After critical freeze-point drying they were sputter coated with gold and examined under a Cambridge scanning electron microscope at an accelerating voltage of 7·5–15 kV.

EXPERIMENT 1

In the first series of experiments six posterior chamber lenses (850b) were suspended in a culture of *Staph. epidermidis* (E004) for 60 minutes. Two lenses were then washed for 60 seconds in 100 ml of fresh broth at 37°C; two lenses were washed in two changes of fresh broth each for 60 seconds; and two lenses were washed in three changes of broth each for 60 seconds. The lenses were then prepared for light microscopy and the number of adherent organisms per high-power field (200×magnification) were determined for 10 fields of view on the plano surface of each lens. Three anterior chamber lenses were incubated in a culture of *Staph. epidermidis* (E001) for 60 minutes: one lens was washed in one change of fresh broth, one lens in two changes, and one lens in three changes and processed for light microscopy and counting.

EXPERIMENT 2

In a further experiment four lenses were incubated in a broth culture of *Staph. epidermidis* (E004) and four lenses in *Staph. epidermidis* (E001). One lens was

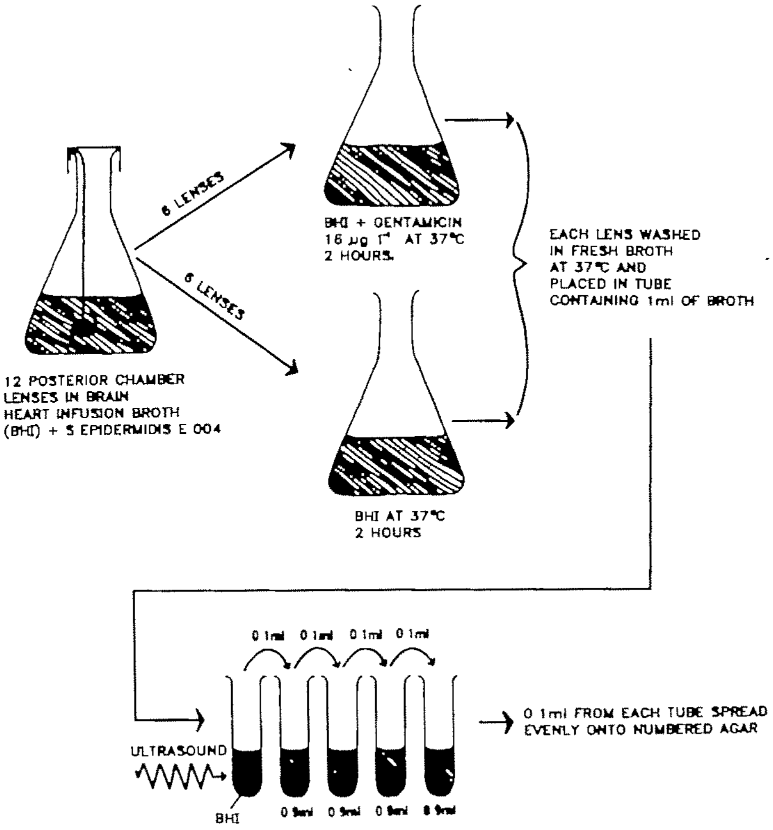

Fig. 1 *Schematic illustration of experiment 1: determination of viable counts.*

removed from each culture at one, two, four, and 16 hours, washed in three changes of broth, and processed for scanning electron microscopy.

EXPERIMENT 3 (Fig. 1)

Twelve Rayner posterior chamber lenses were incubated for 90 minutes in a broth culture of *Staph. epidermidis* (E004). The lenses were removed and washed in fresh broth, six lenses were transferred to a broth containing gentamicin at a concentration of 16 μg l^{-1} at 37°C for 90 minutes; the other six were placed in broth without gentamicin at 37°C for 90 minutes. Three lenses from each group were processed for light microscopy, the remaining lenses were washed in three changes of broth, and each lens was transferred to 1 ml of broth, which was sonicated in a low-power cleaning sonicator for three bursts of 45 seconds each separated by 45 seconds (this regimen was found by prior experiments to remove all the adherent bacteria without affecting their viability). The specimens were vigorously mixed, and the broth containing the dislodged organisms was serially diluted, four times by a factor of 10 each time; 0·1 ml of each dilution was pipetted on to separate nutrient agar plates and spread evenly across the surface of the agar with a sterile wire loop. The plates were incubated overnight at 37°C, and the first plate with a small enough number of colonies to be counted were identified. On the assumption that each colony arises from one organism it is possible to calculate the number of organisms present in the original broth, and therefore on the surface of each lens, by multiplying by the appropriate power of 10. The lenses which had been sonicated were stained for light microscopy to ensure that all adherent organisms had been removed.

Simultaneously 100 ml of *Staph. epidermidis* culture was added to 200 ml of brain heart infusion broth, and gentamicin was added to a concentration of 16 μg l^{-1}. The mixture was incubated at 37°C for 90 minutes, when 5 ml was removed and centrifuged at 2000 rpm for five minutes. The precipitate was resuspended in 1 ml of brain heart infusion broth and serially diluted for viable counting.

Results

EXPERIMENT 1

Slime producing and non-slime producing strains of *Staph. epidermidis* were able to adhere firmly to the surface of intraocular lenses (Table 1). For both strains this was further confirmed by demonstrating that there was no statistically significant difference in the number of attached organisms in lenses washed once, twice, or three times. Some of the adherent organisms were present in groups of two or three, suggesting that they were actively multiplying and colonising the surface of the lenses.

Table 1 *Bacteria counts per high-power field after one, two, or three washes in broth: average of 10 high-power fields with standard deviation in parentheses*

	1 Wash	*2 Washes*	*3 Washes*
Posterior chamber lenses strain E004			
Lens 1	25 (5·0)	32 (9·1)	38 (11·0)
Lens 2	34 (7·0)	21 (7·0)	33 (6·0)
Anterior chamber lenses strain E001			
	19 (4·0)	16 (7·0)	17 (6·0)

Only a few organisms were found to be adherent to the polypropylene haptics in comparison with the surface of the lens. However, the highly curved surface of the loops precluded accurate counting of attached organisms.

EXPERIMENT 2

It was not possible to take sufficient photographs for statistically significant counting, but it was readily apparent that the number of adherent organisms increased the longer the lens remained in broth culture. We have a subjective impression that more organisms were adherent to areas of the lens with surface irregularities (Fig. 2). After four hours of colonisation 'slime' surrounding the colonies was apparent (Fig. 3). The amount of slime increased over the next 12 hours (Fig. 4) and was also present, but in smaller amounts, on lenses colonised by strain E001 after 16 hours.

EXPERIMENT 3

There was an approximately 10-fold reduction in the number of viable organisms attached to the lens

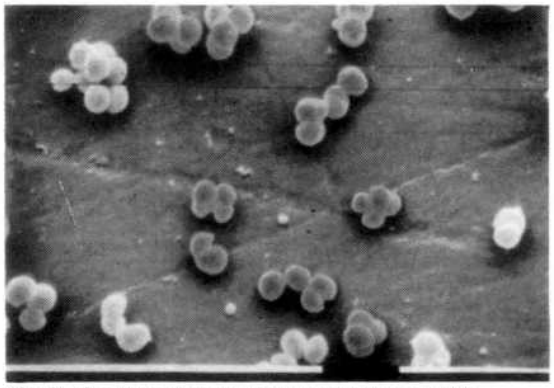

Fig. 2 *Scanning electron microscope photography:* Staph. epidermidis *adherent to the surface of intraocular lens. The organisms appear to be preferentially colonising sites of surface irregularity. Black space bar=2 μm.*

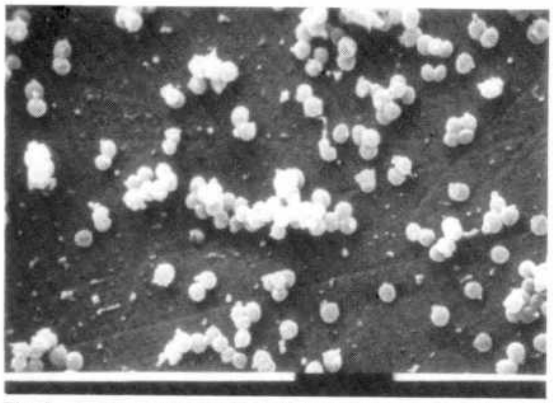

Fig. 3 Staph. epidermidis *(E004) adherent to the surface of an intraocular lens after four hours' incubation. The fluffy material on the surface of some organisms represents the early stages of polysaccharide glycocalyx production. Black space bar=4 μm.*

following gentamicin treatment. The three lenses exposed to gentamicin for two hours had 6000, 1000, and 2000 organisms adhering, compared with 80 000, 40 000, and 70 000 on the untreated lenses. When broth cultures were treated with the same concentration of gentamicin for a similar period of time no viable organisms were recovered.

The lenses processed for light microscopy still had large numbers of adherent organisms irrespective of treatment with gentamicin. The numbers in each high-power field were too great for accurate counting, but there was no subjective difference between the two groups. The lenses which were stained for light microscopy following sonication had only an occasional adherent micro-organism, demonstrating the efficacy of the sonication.

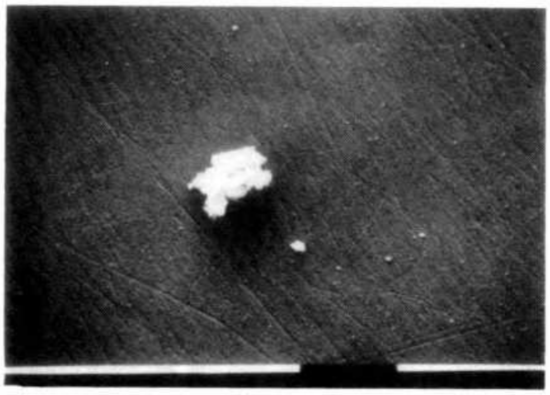

Fig. 4 *Isolated colony of* Staph. epidermidis *(E004) adherent to the surface of an intraocular lens after 16 hours' incubation showing a more extensive polysaccharide coating. Black space bar=10 μm.*

Discussion

The results show that stage 2 adherence of *Staph. epidermidis* to intraocular lenses occurs, as evidenced by the resistance of organisms to removal by washing. Furthermore 'slime' production of *Staph. epidermidis* on the surface of an intraocular lens has been demonstrated for the first time. The appearance of a glycocalyx surrounding the organisms together with the increase in amount with time suggests that it has a major role in adherence to the lens, particularly stage 2.

Surface finish of the lens may also be an important factor in adherence. More organisms appeared to be adherent to areas of irregular surface of the lens than of smooth surface. Previous workers have observed that surface defects provide a locus to which bacteria can initially adhere,[8] and it seems likely that topographical defects of the lens encouraged colonisation.

The concentration of gentamicin found in the anterior chamber after the subconjunctival injection of 20 mg of the antibiotic[9] (16 μg l^{-1}) is sufficient to kill organisms in broth cultures, but it may not be sufficient to kill organisms adherent to the surface of a lens. However, it may be argued that in vivo organisms would not have had time to reach such an advanced state of adherence before being exposed to gentamicin given subconjunctivally at the conclusion of surgery, and that gentamicin is present in the anterior chamber for longer than two hours, though at a lower concentration. The mechanism by which adherence of bacteria to a synthetic surface confers resistance to antibiotics is unclear. However, it has been proposed that the slime coating prevents the antibiotics from gaining access to the organisms.[10] Adherence of bacteria may also protect them from opsonising antibodies.[11]

The role of intraocular lenses as a reservoir of bacteria in endophthalmitis has not been considered before. This study shows that *Staph. epidermidis* is capable of colonising lenses in vitro. Colonisation of lenses by *Staph. epidermidis* may be an important factor in the pathogenesis of endophthalmitis providing a surface to which bacteria can adhere where they are relatively resistant to antibiotics and possibly antibodies. The bacteria may subsequently cross the posterior capsule to multiply in the vitreous humour. It also offers an explanation for cases of localised endophthalmitis which have been described[12] and cases of *Staph. epidermidis* endophthalmitis presenting late and recurring after apparently successful treatment with corticosteroids and antibiotics.[13] If, like other prostheses, intraocular lenses play a part in causing localised infection, there may be new potential approaches for reducing the frequency of endophthalmitis Stage 1 adherence might be reduced by avoiding contact with the conjunctiva during surgery and minimising transient electrostatic charge by washing the lens with balanced salt solution as soon as its container has been opened. Stage 2 adherence presents a more difficult problem, but attention to the surface finish of lenses may be important and materials other than polymethyl methacrylate such as silicone or poly-2-hydroxyethyl methacrylate (P-HEMA), which is less hydrophobic, may also assist in prevention of firm bacterial adherence. More detailed studies of the pathogenesis of endophthalmitis may provide further avenues for the prevention and treatment of this condition.

We thank Rayner Intraocular Lenses Ltd for providing the lenses used in this study, and Mr Angus Parker in the Department of Oral Anatomy at Newcastle University for his assistance with the electron micrographs.

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Accepted for publication 14 July 1988

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topical steroids. Pred Forte contains no antimicrobial agent. If infection is
, appropriate measures must be taken to counteract the infective organisms.
infections of the cornea have been reported coincidentally
ng-term steroid application, and fungal invasion may be
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Product Licence number: 0426/0051.

Date of preparation: February 1988.

Reference 1. Leibowitz HM, Berrospi AR, Kupferman A. Am J of Ophthalmology 1977; **83**(3): 402-406.

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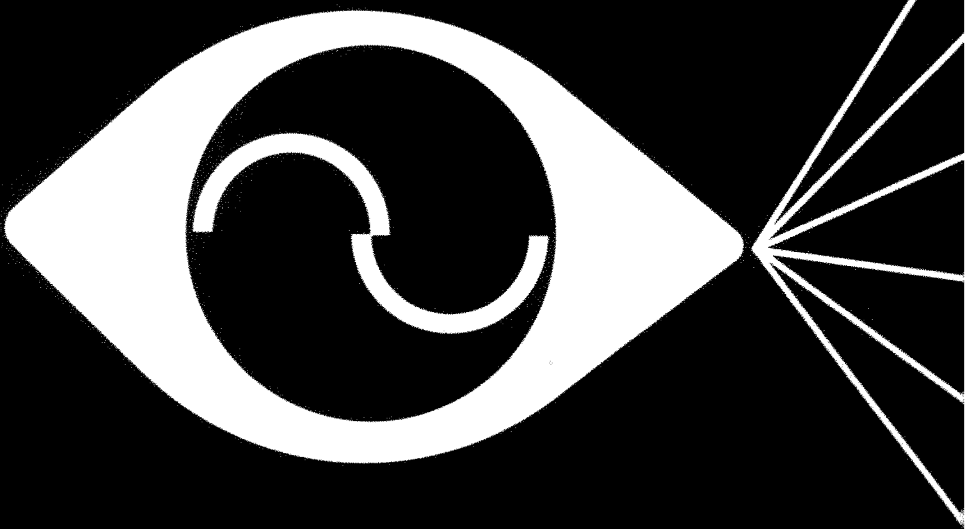
Teoptic

carteolol hydrochloride

eye drops



Topical beta-blocker for the management of glaucoma

DISPERSA

Teoptic: Abbreviated prescribing information

Presentation: Sterile eye-drops containing carteolol hydrochloride 1% or 2% w/v with benzalkonium chloride 0.005% as a preservative. **Uses:** Topical treatment for the reduction of intraocular pressure e.g. in ocular hypertension, chronic open angle glaucoma, some secondary glaucomas. **Dosage and administration:** Initially the recommended adult dose is one drop of Teoptic 1% Eye-drops in affected eye twice daily. If required the dosage may be altered to one drop of Teoptic 2% Eye-drops in affected eye twice daily. *Children:* Use not recommended. *Elderly patients:* Recommended adult dose suitable. **Contra-indications:** Uncontrolled cardiac insufficiency. Bronchospasm, bronchial asthma, chronic obstructive pulmonary disease. Pregnancy. Hypersensitivity. **Precautions:** As with other topically applied ophthalmic preparations, Teoptic may be absorbed systemically. Therefore Teoptic should be used with caution in patients receiving systemic beta-blockers or with known contra-indications to systemic beta-blockers e.g. sinus bradycardia, second and third degree block, cardiogenic shock, uncontrolled diabetes.

Offers protection of visual function

Significant reduction in IOP levels

Well tolerated locally and systemically

Content of benzalkonium chloride only 0.005%

pH value 6·7

Five good reasons for prescribing Teoptic

As with all ophthalmic preparations containing benzalkonium chloride, soft or gas-permeable contact lenses should not be worn during treatment. **Side effects:** Ocular reactions such as irritation, burning, pain, blurred vision, conjunctival hyperaemia and corneal disorders such as keratitis may occasionally develop. As with all beta-blockers bradycardia, dyspnoea, headache, lassitude and vertigo have occasionally been reported. **Breast feeding:** Teoptic may be systemically absorbed and penetrate the breast milk. Use in lactating mothers should therefore be at the discretion of the physician. **Basic NHS Cost and Product Licence Numbers:** Teoptic 1% Eye-Drops £5.05 per 5ml bottle (0030/0040) Teoptic 2% Eye-Drops £5.67 per 5ml bottle (0030/0041). **Product Licence holder:** Dispersa, Westhead, 10 West Street, Alderley Edge, Cheshire SK9 7XP. Further information is available on request to the above address.

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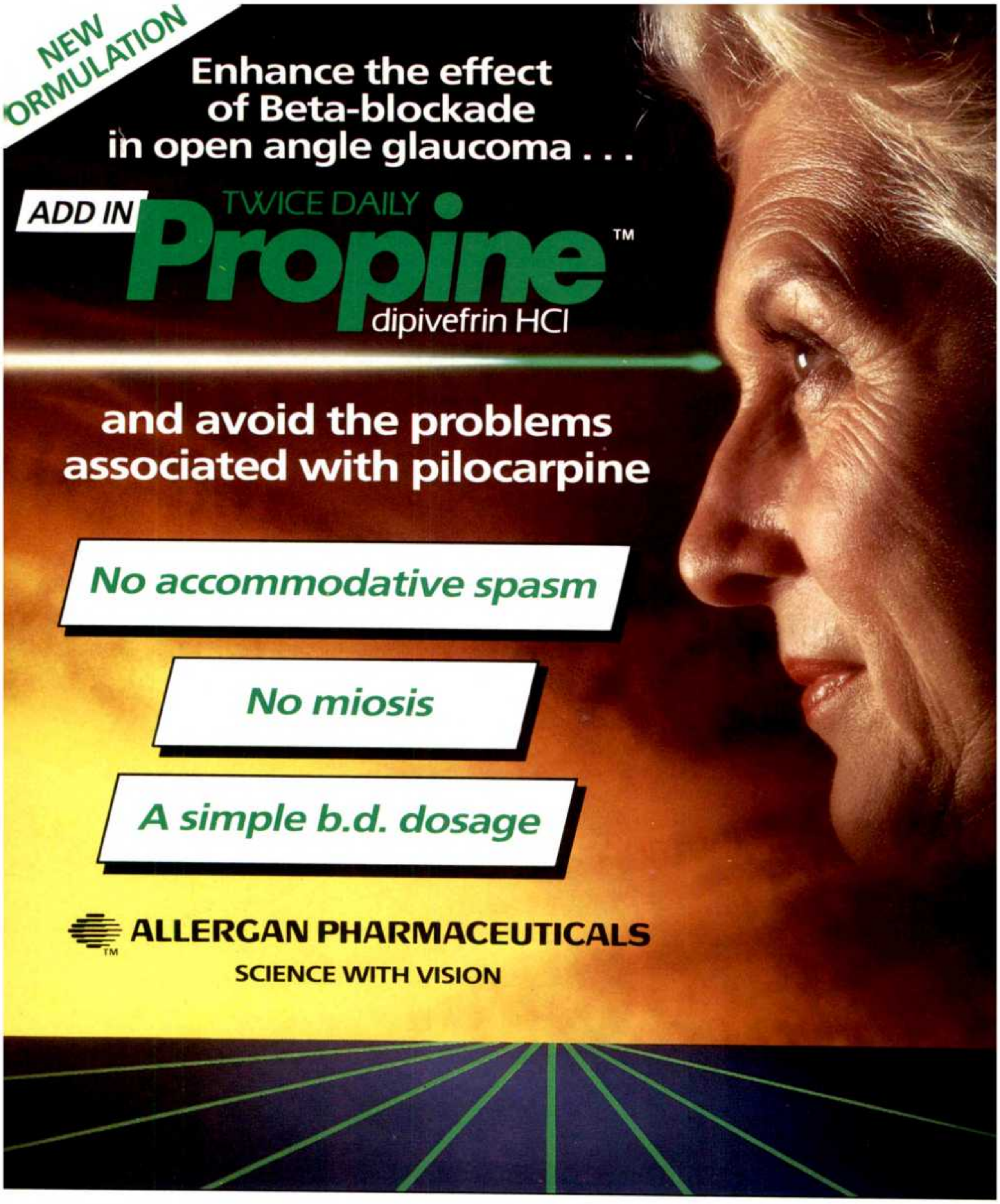

PROPINE™ Prescribing Information
Presentation Sterile ophthalmic solution containing dipivefrin hydrochloride USP 0.1% (w/v). Also contains benzalkonium chloride Ph Eur 0.005% (w/v), disodium edetate Ph Eur 0.015% (w/v), with sodium chloride Ph Eur and purified water Ph Eur. **Uses** For the control of intraocular pressure in chronic open angle glaucoma or ocular hypertensive patients with anterior chamber open angles. **Dosage and administration** The usual dosage is one drop in the affected eye(s) every 12 hours. **Contra-indications, warnings, etc.** *Contra-indications:* patients suffering from closed angle glaucoma. *Use in pregnancy:* the safety of intensive or protracted use of dipivefrin during pregnancy has not been substantiated. *Precautions:* dipivefrin should be used with caution in patients with narrow angles since dilation of the pupil may trigger an attack of angle closure glaucoma. Macular oedema is a rare occurrence with adrenaline use in aphakic patients. Prompt reversal generally follows discontinuance of the drug. Macular oedema with dipivefrin does present as a possibility in the aphakic patient. *Adverse reactions:* rebound vasodilation and allergic blepharoconjunctivitis are rarely observed following treatment with dipivefrin. Dipivefrin has been used successfully in patients who demonstrated such intolerance to adrenaline. Adrenochrome deposits have been rarely observed following use of dipivefrin. Very slight transitory stinging may occur upon instillation in some patients. This product contains benzalkonium chloride and should not be used by patients continuing to wear soft (hydrophilic) contact lenses. **Pharmaceutical precautions** Store at room temperature. Discard any unused contents 28 days after opening the bottle. **Legal category** POM.
Package quantities Plastic dropper bottle containing 10ml.
Further information Nil. **Basic NHS Cost:** (as at October 1988) £4.65.
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Retention of iris supported intraocular lenses at the time of penetrating keratoplasty for pseudophakic corneal oedema

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SUMMARY The long-term follow-up of patients undergoing penetrating keratoplasty for pseudophakic corneal oedema is reported. The cause and frequency of corneal decompensation following intracapsular cataract extraction with insertion of an iris supported lens was assessed and found to be unrelated to the implant in the majority of cases. The most common cause of decompensation was endothelial touch during the cataract extraction. In all eyes the intraocular lens was retained at the time of penetrating keratoplasty. The hazards of removal of the lens are discussed and the recommendations made that lenses be retained when penetrating keratoplasty is undertaken for pseudophakic corneal oedema, other than in exceptional cases.

Pseudophakic corneal oedema is one of the leading indications for penetrating keratoplasty.[1 2] Its incidence may be higher in intracapsular cataract extraction with insertion of an iris clip lens than in extracapsular surgery with a posterior chamber lens.[3]

This has led to the false assumption that the continued presence of an iris supported lens in the eye after penetrating keratoplasty will necessarily prejudice the survival of a corneal graft. Some authors have recommended that all iris supported lenses be removed at the time of penetrating keratoplasty for pseudophakic corneal oedema,[1] though this remains a controversial issue.[4]

We present the results of follow-up of all the patients under the care of the senior author and who required penetrating keratoplasty for pseudophakic corneal oedema in the presence of an iris supported lens over the period 1971–84. Particular attention is drawn to the original cause of endothelial decompensation necessitating the graft and of the subsequent survival of the graft in patients retaining the iris supported lens.

The results lead to the conclusion that removal of the intraocular lens is contraindicated except when conditions exist causing a shallow anterior chamber, with the resulting risk of endothelial touch.

Materials and methods

The records of 675 cases of intracapsular cataract extraction with the placement of a Binkhorst four-loop lens performed during the period 1971–84 were studied. The incidence of postoperative endothelial decompensation was noted as well as that of peroperative endothelial touch. The patients who subsequently underwent penetrating keratoplasty for corneal oedema from whatever cause were reviewed and the cause of their endothelial decompensation recorded.

All cataract surgery was performed by a standard technique, described by the senior author,[5] with the use of chymotrypsin prior to cryoextraction of the lens. The intraocular lens was placed obliquely and, for maximum stability, prevented from rotating by a single iris suture round the upper, anterior loop of the lens. Two peripheral iridotomies were made.

The subsequent corneal grafting was undertaken by a number of surgeons, using either 16 interrupted 10/0 sutures or a combination of eight interrupted and one continuous. In all patients the intraocular lens was retained at the time of keratoplasty. In one patient an adhesion between the lens loop suture and the cornea was divided, and in another the anterior loops of the lens were removed owing to the shallowness of the anterior chamber and the suspicion of touch of the corneal endothelium. A further two patients had an extra 10/0 Prolene suture inserted to fix the inferior lens loop to the iris, for increased stability. One patient required a limited anterior vitrectomy owing to herniation of vitreous through the peripheral iridotomies at the time of

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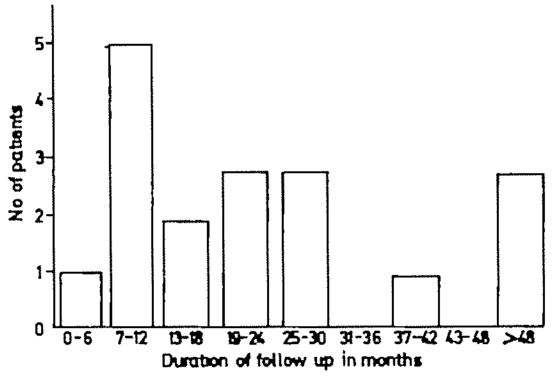

Fig. 1 *Distribution of duration of follow-up after keratoplasty.*

keratoplasty. No vitreous was present in the anterior chamber in the other cases.

The patients and their notes were reviewed between 6 and 70 months after keratoplasty (mean 24·5 months). Details of follow-up period are shown in Fig. 1. In all cases the endothelial status as assessed prior to cataract extraction was noted, the time following surgery at which endothelial decompensation was first noted, and the suspected factors contributing to it. The per- and postoperative complications of cataract surgery were studied and the current state of the corneal graft and visual acuity. The presence or absence of clinical cystoid macular oedema was recorded, as defined by the presence of visible macular oedema in association with reduction of visual acuity to 6/12 or below.

Results

Of 675 cataract extractions, endothelial decompensation causing a reduction of visual acuity to less than 6/12, and hence requiring penetrating keratoplasty, developed in 18 The reasons for the corneal decompensation following cataract surgery are listed in Table 1. The commonest cause was peroperative endothelial touch, the occurrence of which was always specifically recorded in the operation notes. Although endothelial touch was recorded in 35 of the 675 operations, it led to endothelial decompensation affecting vision in only six of the eyes, and the other 29 cases in which touch was recorded have not subsequently decompensated.

Table 1 *Causes of corneal decompensation, and time in months following cataract extraction of its occurrence*

Cause of decompensation	*No. of patients*	*Time postop (mean in months)*
Lens suture touching endothelium	1	64
Pupil block or shallow anterior chamber causing lens-corneal touch	3	14
Peroperative endothelial touch	6	35
Raised intraocular pressure	4	44
Pre-existing endothelial corneal dystrophy	3	24
Loop dislocation	1	130

Table 2 *Reasons for failure of four corneal grafts*

Patient	*Reason for failure*
1	Endothelial failure secondary to raised intraocular pressure; herpes simplex infection
2	Immunological graft rejection
3	Peripheral anterior synechiae pulling lens loop to corneal endothelium
4	Lens touch due to postkeratoplasty wound leak and shallowing of the anterior chamber

It is interesting to note that all six eyes had been operated on prior to the widespread use of sodium hyaluronate. It is also of importance that peroperative endothelial trauma is not usually immediately manifest: indeed the mean time between surgery and the first signs of decompensation was 35 months. Study of all intracapsular cataract extractions with insertion of Binkhorst lenses and followed up for more than five years showed some endothelial corneal decompensation in 2·1% of eyes at two years and 6·6% at five years. It was often peripheral only, and did not affect visual acuity. Clinically significant corneal decompensation, defined as that causing a reduction in visual acuity to less than 6/12, occurred in only 18 patients and was treated with penetrating keratoplasty

The corneal graft remained clear and without further problems in 14 of the 18 patients. The reasons for graft failure in the other four are shown in Table 2. The two patients whose grafts opacified owing to raised intraocular pressure together with, respectively, herpes simplex infection and graft rejection, had successful repeat keratoplasty. The former achieved 6/60+1 acuity only, as a result of extensive

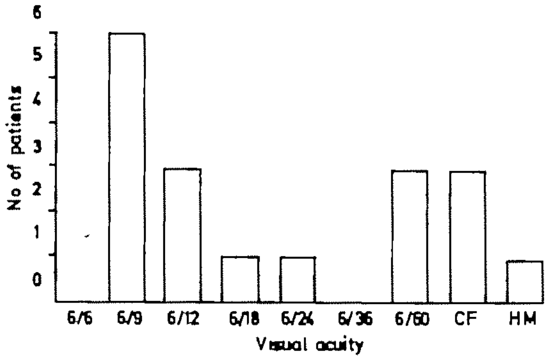

Fig. 2 *Current corrected visual acuity.*

glaucomatous nerve damage, and the latter 6/24, acuity being limited by the presence of cystoid macular oedema.

One of the other two patients declined repeat keratoplasty, and the other is awaiting surgery.

The current visual acuity of all 18 patients is shown in Fig. 2, and the reasons for poor vision in those achieving less than 6/12 are summarised in Table 3.

Discussion

The results of the study highlight a number of features of relevance to the management of pseudophakic corneal oedema. The first is that corneal oedema severe enough to require penetrating keratoplasty is a relatively uncommon complication of intracapsular cataract extraction with insertion of an iris supported lens (2·7%), and that in most cases factors other than the intraocular lens appeared to be responsible for the endothelial decompensation. These included peroperative touch, pre-existing corneal disease, and raised intraocular pressure prior to cataract extraction. The incidence here of pseudophakic corneal oedema compares favourably with that of the combined experience of a number of authors of 3·6%.[4] Although the incidence of endothelial touch was 35 out of 675 (5·2%), in only six cases (0·9%) did this subsequently cause clinically significant corneal oedema. In those cases in which the intraocular lens did appear to have contributed, the problem was remediable without recourse to removal of the lens. For example, in one patient the suture retaining the lens was intermittently touching the corneal endothelium, and it was possible to trim this at the time of keratoplasty; in two other patients an unstable lens was stabilised by an additional suture through the lower, anterior lens loop.

Indeed, the hazards of attempted removal of a lens are considerable. Hall and Muenzler,[7] in removing 53 intraocular lenses from patients with pseudophakic corneal oedema, needed to perform anterior vitrectomy in all but two. Waring *et al.*, in removing all intraocular lenses at keratoplasty, achieved a final visual acuity of 6/12 or better in only 16%.[8] Arentsen and Laibson also found a better prognosis if the intraocular lens was retained.[9] Busin *et al.*[10] pointed out the increased incidence of cystoid macular oedema when vitreous is removed, a fact which had been previously suggested by a number of authors.[11–14] The risk of retinal detachment is also increased. Waring stressed the importance of careful peroperative examination of an intraocular lens prior to deciding whether to remove it, including retraction of the iris to inspect the posterior loops and inspection of the angle either with a dental mirror or by inversion of the limbus.[15]

Table 3 *Reasons for visual acuity of less than 6/12 after keratoplasty*

Pathology	*No of patients*
Cystoid macular oedema	2
Glaucomatous nerve damage	2
Age related macular degeneration	2
Diabetic maculopathy	1
Opaque corneal graft	2

The term pseudophakic corneal oedema is defined as 'irreversible corneal oedema in an aphakic eye with an intraocular lens'. It does not imply that the lens is responsible for the oedema but simply that it is witness to it. Though it would be fallacious to suggest that the iris supported lens is never responsible for pseudophakic corneal oedema, it is equally imprudent to remove such a lens indiscriminately, without thought as to both the necessity of doing so and the potential hazards involved.

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Clinicopathological findings in a growing optic nerve melanocytoma

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SUMMARY We present an unusual case of a melanocytoma of the optic disc that showed documented progressive growth over a period of six years. It reached the largest size of any reported optic nerve melanocytoma and the eye was enucleated because of the possibility of malignant degeneration. Optic nerve melanocytomas are locally invasive but are not known to undergo transformation into malignant melanoma. Follow-up should remain the primary approach in the management of patients with optic nerve melanocytomas, as previously advocated by Zimmerman.

The management of melanocytomas of the optic disc has changed over the past two decades from enucleation to simple serial observation. Before the pioneering work of Zimmerman,[1-4] deeply pigmented lesions of the optic nerve were considered to be primary malignant melanomas of the optic disc.[5] Loewenstein suggested that such lesions may represent malignant transformation in a naevus of the optic nerve.[6] DeVeer reviewed the literature related to malignant melanoma of the optic nerve and doubted the existence of a primary malignant melanoma of the disc, as most of the reported lesions showed a peripapillary origin.[7] Seven years later DeVeer examined an eye enucleated for a so-called malignant melanoma of the optic nerve. The cells did not appear to be anaplastic, and he concluded that this lesion is benign despite its infiltration into the retina and the optic nerve.[8]

As a result of a large clinical and histopathological study of such lesions with long-term follow-up Zimmerman established the entity of 'melanocytomas', choosing this term in part to indicate the benign behaviour of the darkly pigmented tumour of the optic disc.[1-4] Subsequently Cogan coined the term 'magnocellular nevus'[9] and Reese the term 'benign melanoma' to describe the same lesion.[10] Melanocytomas are now thought to be predominantly stable lesions with no malignant potential.[11]

We present the first clinicopathological study of an optic nerve melanocytoma with prominent growth that led to enucleation of the eye because of suspected malignant transformation. This case along with a review of the literature helps to establish the point that there is no documented case of malignant change in optic nerve melanocytomas, and that growth in these tumours reflects simply their locally invasive behaviour.

Case report

The patient was a 42-year-old fair-complexioned Causasian man who presented for routine physical examination in February 1968. The physical examination gave essentially negative results except for mild systemic hypertension and a pigmented right optic disc. In April 1968 he presented to his local ophthalmologist with the complaint of sensitivity to light in the right eye. An eye examination revealed 20/20 vision bilaterally, enlarged right blind spot, and a pigmented lesion over the right optic disc. An examination in May 1968 gave unchanged results, but

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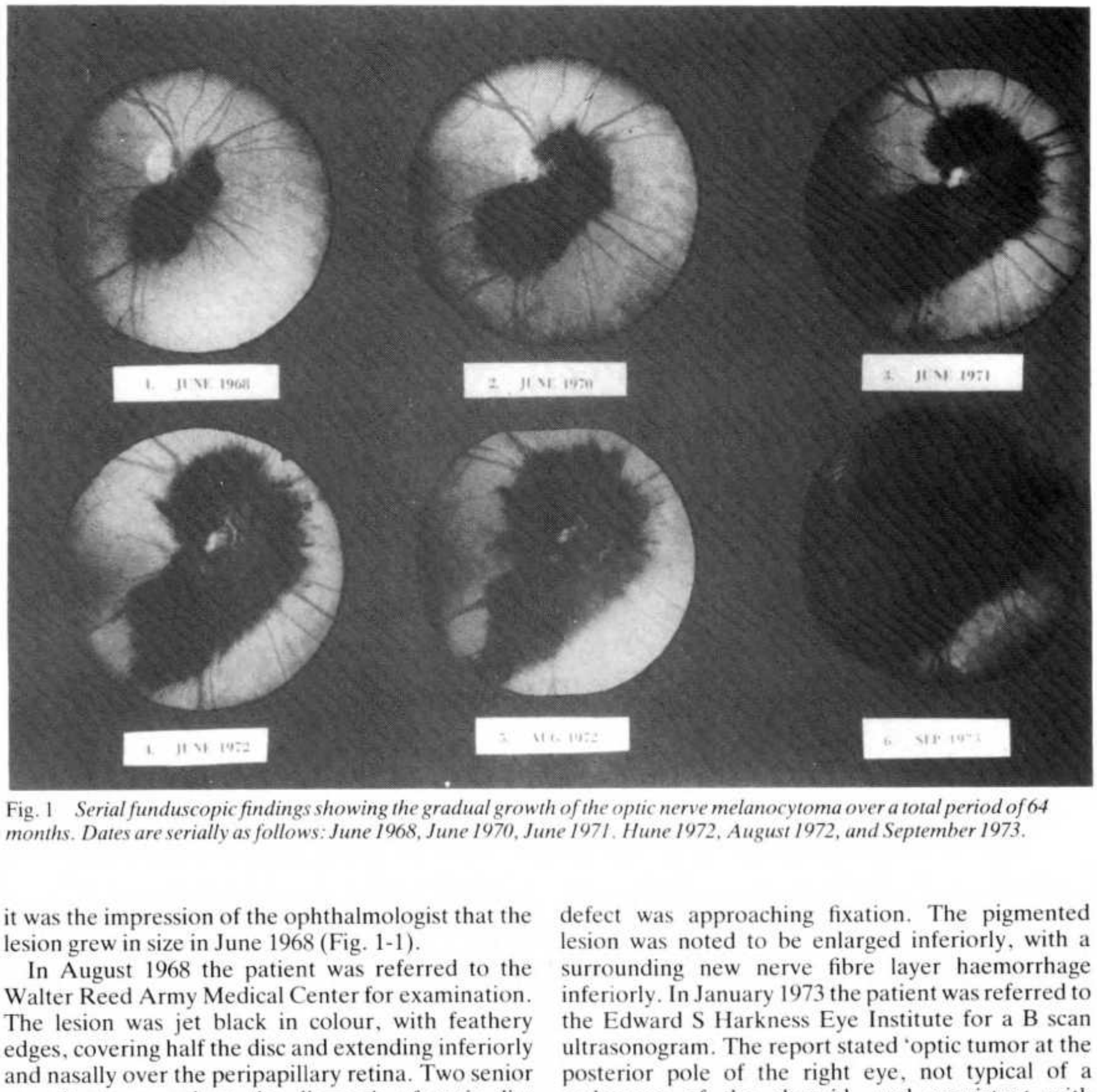

Fig. 1 *Serial funduscopic findings showing the gradual growth of the optic nerve melanocytoma over a total period of 64 months. Dates are serially as follows: June 1968, June 1970, June 1971. Hune 1972, August 1972, and September 1973.*

it was the impression of the ophthalmologist that the lesion grew in size in June 1968 (Fig. 1-1).

In August 1968 the patient was referred to the Walter Reed Army Medical Center for examination. The lesion was jet black in colour, with feathery edges, covering half the disc and extending inferiorly and nasally over the peripapillary retina. Two senior consultants agreed on the diagnosis of optic disc melanocytoma and recommended periodic observation. At follow-up in June of 1970 there was enlargement of both the pigmented lesion and the visual field defect (Fig. 1-2). Vision was 20/20−1 in the right eye. During subsequent visits in June 1971 (Fig. 1-3) and June 1972 (Fig. 1-4) further enlargement of the lesion, progressive obscuration of the disc, and scattering of pigment clumps into the adjacent retinal nerve fibre layer were noted. In August 1972 (Fig. 1-5) a nerve fibre layer haemorrhage was observed adjacent to the tumour temporally. This cleared over the following two months. In December 1972 the patient complained of 'foggy vision'. His vision remained 20/20 in the right eye. An enlarging field defect was approaching fixation. The pigmented lesion was noted to be enlarged inferiorly, with a surrounding new nerve fibre layer haemorrhage inferiorly. In January 1973 the patient was referred to the Edward S Harkness Eye Institute for a B scan ultrasonogram. The report stated 'optic tumor at the posterior pole of the right eye, not typical of a melanoma of the choroid, and consistent with melanocytoma.' The dimensions of the lesion as determined by ultrasonography were 1·5 mm in elevation, 6 mm in diameter, and with evidence of extension of the tumour posterior to the cribriform plate.

In February 1973 the vision was 20/20−2, with the optic disc becoming almost totally obscured by the pigmented lesion. Fluorescein angiography revealed blockage of fluorescence of both the choroidal and retinal vasculatures by the mass, with absence of leakage around the mass. In September 1973 (Fig. 1-6) the patient presented with decreased vision and floaters in the right eye. Vision in the right eye was 20/40+2. There was a mild afferent pupillary defect.

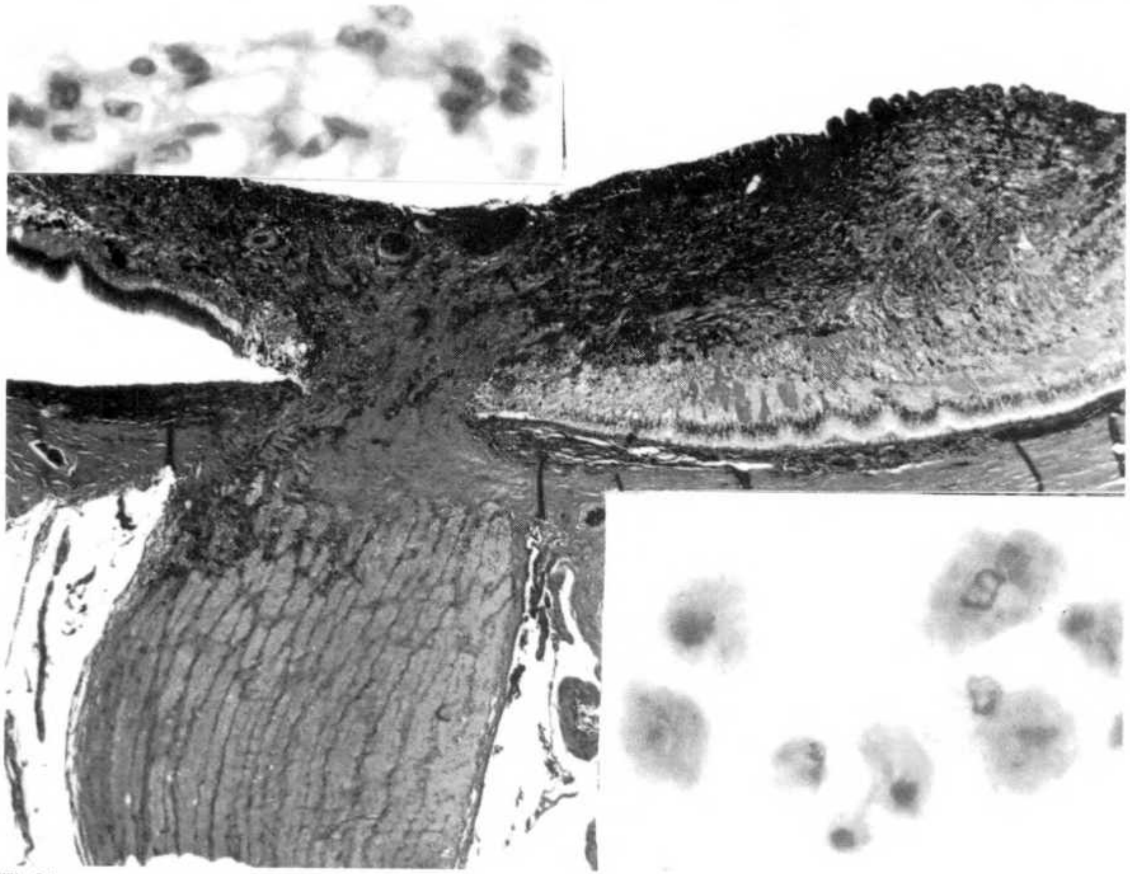

Fig 2A

Fig. 2 *Histological sections through the optic nerve and macula.* A: *Cross section of the posterior pole reveals small groups of pigmented cells extending to the level of the lamina cribrosa and behind the lamina nasally. The nasal juxtapapillary choroid is similarly involved. The peripapillary retina is diffusely thickened especially temporally from tumour infiltration. Haematoxylin and eosin, ×7. The tumour is formed of small spindle cells (upper inset, haematoxyling and eosin, bleached preparation, ×600), large polyhedral heavily pigmented cells (lower inset, haematoxylin and eosin, bleached preparation, ×600), and pigment laden macrophages.* B: *Section through the fovea reveals a detachment of the retina by proteinaceous exudate. There is diffuse infiltration of the retina by pigmented cells with involvement of the retinal surface and formation of an epiretinal membrane. Large cystoid spaces in the outer plexiform layer are filled with proteinaceous material and pigment laden macrophages. Haematoxylin and eosin, ×60.*

Dispersed brown and black pigments were noted in the vitreous cavity, with layering along the inferior surface of the posterior lens capsule. The tumour had increased in its anteroposterior thickness. There was further encroachment of the field defect on fixation.

In April 1974 the patient reported a drastic decrease in vision. Vision was 20/100−1, and the enlarging scotoma had covered fixation by visual field testing. The lesion had enlarged, and exudates were observed in the macula. No dye leakage was noted on fluorescein angiography. Because of the possibility of a malignant melanoma arising in a melanocytoma, enucleation was advised. A P-32 test with readings taken at the time of enucleation was negative. The patient remained healthy on his last medical visit in March 1986.

HISTOPATHOLOGICAL DESCRIPTION

On gross examination the specimen was seen to consist of a right eyeball with 13 mm segment of attached optic nerve. Transillumination of the eye and optic nerve revealed no definite shadow. The external examination of the eye revealed no abnormality. A cross section of the optic nerve 1 mm from

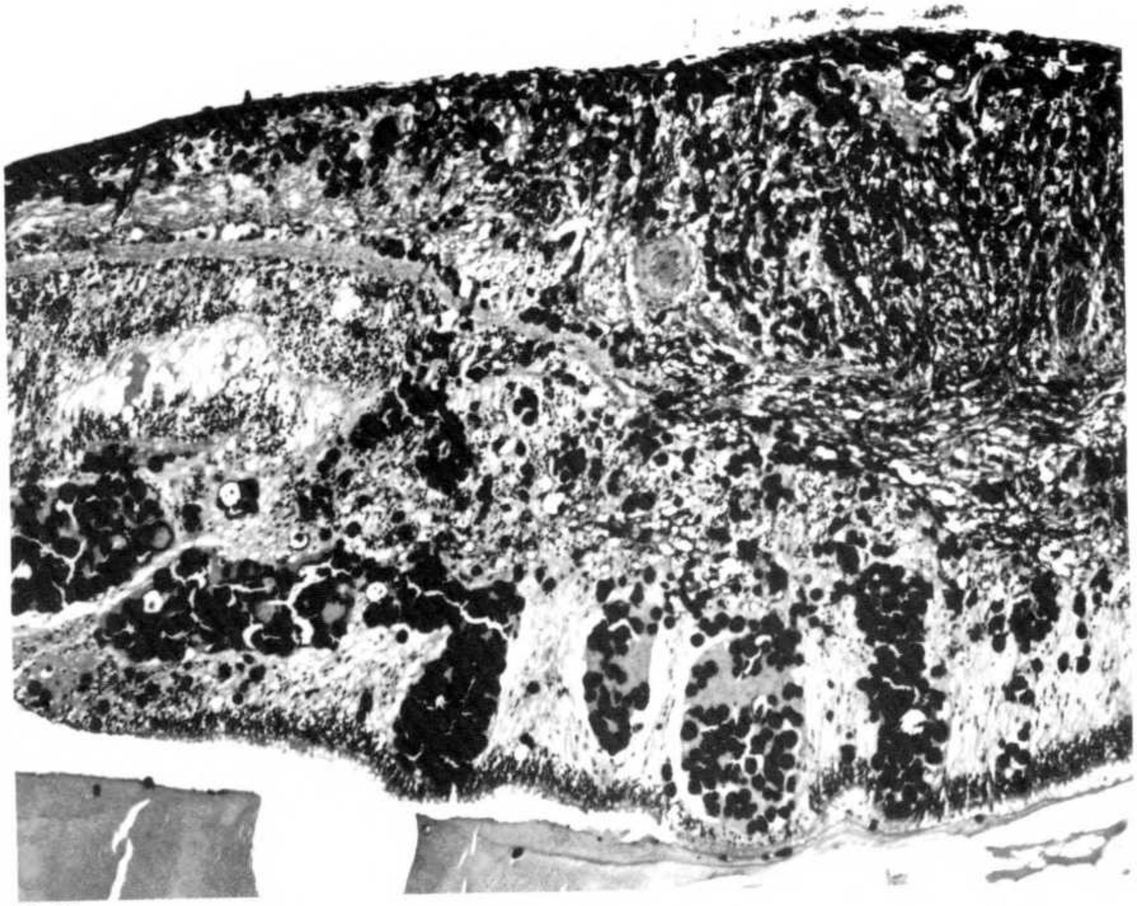

Fig. 2B

the sclera revealed no evidence of pigmentation.

The globe was opened horizontally through the optic nerve, revealing a heavily pigmented tumour covering the optic disc and measuring 7 mm in greatest horizontal dimension. The tumour was raised by a coagulated subretinal exudate. Yellowish intraretinal exudates were present along the temporal edge of the tumour. Pigmented deposits were present in the subretinal space at the temporal edge of the optic disc. Very little tumour was seen deep in the optic nerve head except for a small patch of intense pigmentation behind the lamina cribrosa nasally. The vitreous was detached posteriorly and contained large pigmentary deposits. Moderate pigmentation and thickening of the nasal peripapillary choroid was noted. The pigmented tumour had spread into the bulging juxtapapillary retina inferiorly and superiorly. Two patches of superficial retinal haemorrhages were noted superiorly.

On microscopic examination (Figs. 2A, B) the anterior segment was unremarkable except for the presence of several foci of free pigment granules adherent to the posterior lens capsule, zonular fibres, and anterior hyaloid surface. Moderately heavy pigmentation of the uveal tract was most pronounced posteriorly. Within the optic nerve and extending into the peripapillary area was a very heavily pigmented tumour. The tumour lay superficially in the optic nerve, though small groups of pigmented cells extended to the level of the lamina cribrosa and a short distance behind the lamina nasally. The nasal juxtapapillary choroid showed only a small amount of tumour. The tumour involved the juxtapapillary retina more extensively in the temporal side, where it replaced most of the nasal half of the macula.

The fovea was detached by a large accumulation of proteinaceous subretinal exudate containing heavily pigmented macrophages. There was a large accumulation of serous exudate and foamy histiocytes in the outer plexiform layer of the foveal region. Between the disc and the fovea the retina was severely thickened, measuring 1·5 mm in thickness as the result of the massive infiltration by the pigmented cells. These cells included a mixture of heavily pigmented polyhedral melanocytes with round, ovoid, and evenly chromatic nuclei like those found in melanocytomas, large rounded melanophages, and smaller pigmented spindle cells with irregular, vesicular, and hyperchromatic nuclei resembling the spindle A melanoma cells of the iris. The spindle cells were the predominant cells at the junction between the tumour and normal retina nasally.

The internal limiting membrane was infiltrated in the temporal peripapillary area by the pigmented cells to form a thin placoid pigmented layer along the inner retinal surface. Tumour cells infiltrated along the retinal vessels in the peripapillary area and the major vessels in the optic nerve head. No tumour was noted in the cross sections of the optic nerve, meninges, or orbital tissues. Special stains revealed dropout of axons and foci of demyelinisation, especially on the temporal side of the optic nerve.

Transmission electron microscopic findings have been reported previously.[12]

The final pathological diagnosis was melanocytoma of the optic nerve head.

Discussion

Several features in our case are typical of an optic nerve melanocytoma. They include the jet black colouration, the feathery edges, the origin from the optic disc as noted on initial presentation, the relatively well preserved vision and visual fields for a long period of follow-up, and the findings on ultrasonography and fluorescein angiography. Unusual features include the relatively very large size of the mass, its growth pattern, infiltration of the macular region, the presence of retinal haemorrhages, and the formation of a preretinal pigmented plaque.

Melanocytomas of the optic nerve have been characterised as stable or slowly growing lesions.[11] A total of 38 cases followed up for five years or more showed no evidence of growth[3, 13-15] and no evidence of metastasis following enucleation.[3] Joffe *et al.*[11] followed up 27 cases for more than one year and found no change in size in 22 eyes. Mild enlargement of the melanocytoma has been recorded in a total of 11 cases,[3, 10, 11, 16, 17] usually after several years of follow-up. The average size of the lesion was calculated from the series of 40 cases reported by Joffe *et al.* to be around 40% of the optic disc size.[11] Complete obscuration of the optic disc was found in nine cases.[3, 10, 11, 18] The three largest reported tumours were around 2 disc diameters in diameter.[3, 11, 18]

The pattern of growth in the occasionally expanding melanocytomas is not known. In one case the tumour grew progressively over a period of seven years and became stationary over the next eight years of follow-up.[3] In another case the tumour seemed to grow over a period of one week.[3] Malignant melanoma arising in a melanocytoma of the uveal tract had been encountered in several of the cases seen at the Ophthalmic Registry of the Armed Forces of Pathology, and in several case reports.[19, 20] However, there is still no documented case of a malignant melanoma arising from an optic nerve melanocytoma. Apple *et al.*[21] described the first case of malignant transformation of an optic nerve melanocytoma. However, the initial grey mass at the superior aspect of the disc was not recorded and seemed atypical in location and discolouration for a primary optic nerve melanocytoma favouring a peripapillary choroidal origin. Moreover it was not clear if the melanoma arose originally from the choroidal or the optic nerve part of the naevus. It has been estimated that there is one in 5000 chance for a choroidal naevus to develop into a malignant melanoma.[22] If this is applied to the optic nerve melanocytoma, an uncommon form of naevus, malignant transformation would be extremely rare. Growth in melanocytomas reflects their known locally invasive behaviour.[3]

The causes of visual loss in melanocytomas of the optic disc are multiple. There have been seven cases of decreased vision from 20/50 or less[2, 3, 8, 11, 23] up to hand motion[3] and to no light perception,[16] with two of these cases having a sudden loss of vision.[3, 16] Papilloedema followed by occlusion of the central retinal artery was the initial manifestation of a deeply seated optic nerve melanocytoma.[16] Similarly, ocular pain was the presenting sign of a partially necrotic optic nerve melanocytoma that showed vaso-occlusive disease of the optic nerve, ischaemic necrosis of the tumour, hypoxic retinopathy, and neovascular glaucoma.[24] Zimmerman[3] described one case showing ischaemic necrosis of an optic nerve melanocytoma that invaded deeply into the nerve and was related to an occlusion of an anomalous vascular supply to the tumour and temporal retina. Loss of vision with subsequent progressive partial recovery was described in one case of optic nerve melanocytoma, though the mechanisms of recovery were not clear.[15] Disciform scarring over a choroidal melanocytoma may lead to decrease in vision and simulate a choroidal melanoma.[25] No disciform lesion has been seen overlying an optic disc melanocytoma.

Despite these isolated reports, the major cause of decreased vision is attributed to the swelling of axons from compression of the nerve fibres and their vascular supply by the tumour.[26] This explains why deeply seated optic nerve melanocytomas, despite their small apparent size, may result in visual loss.[3,4] Computed tomography and ultrasonography can help in delineating the posterior extension of melanocytomas, and such investigations should be carried out if the visual symptoms are not commensurate with the fundus picture. Sectorial optic nerve atrophy in such lesions has been demonstrated histopathologically.[27] Direct infiltration of the nerve fibre layer by the mass, along with pressure atrophy of the nerve axons, can explain the not infrequent occurrence of nasal steps, arcuate nerve fibre layer visual defects, and the Marcus Gunn pupillary sign in optic nerve melanocytomas. Our case is unique in that the nasal macula was infiltrated by the tumour and the temporal macula was elevated by a serous subretinal fluid. Moreover the surface of the macula was covered by a pigmented layer and pigment dispersion from the melanocytoma was found in the anterior aspect of the posterior segment. This dispersion of pigment granules and pigmented cells should not be taken as a sign of active tumour growth, as previously noted by Reese.[10]

This work was supported by a UNESCO research grant (Dr Mansour)

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Treatment of ptosis by levator resection with adjustable sutures via the anterior approach

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SUMMARY The authors describe a one-step anterior approach levator resection technique with intraoperative adjustable sutures. Forty-four ptotic eyes were divided into five groups, and the results of this technique were evaluated for each of these five types of ptoses. Our results show that it is not possible to predict the extent of a levator resection preoperatively from the assessment of the levator function and degree of ptosis. We therefore propose this flexible method as the operation of choice for the correction of senile, traumatic and congenital ptosis.

The fact that over 100 techniques for the treatment of ptosis have been reported[1-3] illustrates that ptosis appears to be difficult to treat, as the postoperative eyelid position is highly unpredictable. We also experienced this in the series of patients presented here. In most cases the anterior approach levator resection technique as described by Beard[4] was used. According to this method the amount of levator muscle resection is determined before starting the operation and depends on the levator function and the amount of ptosis. In our hands, however, this method caused largely unforeseen postoperative results.

Some surgeons therefore introduced the posterior levator approach[5] because it opens up the possibility of postoperative adjustment by leaving the sutures in place longer for the cases of undercorrection or removing them earlier if the eyelid is too high postoperatively. We decided to use the anterior approach levator resection technique because it is both easier from the anatomical point of view and leaves the conjunctival surface of the lid (area of accessory lacrimal glands) untouched.

The unpredictable postoperative results formed a strong stimulus to look for a more flexible method to determine the amount of muscle to be resected. In this paper we present our results with an anterior approach levator resection technique with intraoperative adjustable sutures. The amount of levator resection can be determined during the course of the operation, after a provisional fixation of the levator muscle. But to obtain satisfactory results treatment under local anaesthesia is essential.

Before the actual muscle resection is performed the knots are tied and the patient is asked to look straight ahead so that we may evaluate the functional result that can be expected postoperatively. If the position of the eyelid still appears to be too low or too high, the sutures are repositioned in the levator muscle until a good position of the eyelid is achieved. Only then is the actual resection of the levator muscle performed. The patients were selected exclusively on the basis of the amount of ptosis (exceeding 2 mm) and levator function (exceeding 3 mm). With this modified levator resection technique with adjustable sutures 86% of the patients with different causes of ptosis had a cosmetically good result after only one surgical procedure.

Material and methods

The analysis of the amount of ptosis, which is the difference in mm between the interpalpebral fissures of the eyes and the amount of levator function, was done with a small ruler. The levator function is expressed as the distance in mm of the superior eyelid between maximal downgaze and upgaze. The frontal muscle should not contribute to this eyelid movement. Its function is checked by pressing the examiner's thumb against the eyebrow while measuring the levator function.

ANTERIOR APPROACH LEVATOR RESECTION TECHNIQUE

A horizontal line is drawn on the eyelid at about 7 mm from the lid margin to mark the place of the future skin crease. After eversion of the superior

Correspondence to Dr H A Hylkema

eyelid 2 ml of lignocaine 2% with epinephrine is injected into the subconjunctival area. Thus the conjunctiva is separated from Müller's muscle. The upper eyelid is then further anaesthetised subcutaneously with approximately 3 ml of local anaesthetic. A horizontal incision in the skin crease is made through the skin-muscle layer parallel to the muscle fibres on to the tarsal plate. By going upwards in the direction of the upper roof of the orbit the orbital septum is visualised. The septum is opened, the orbital fat is freed, and below the fat the levator muscle is identified. The levator muscle is freed from Müller's muscle. Muller's muscle is not resected. Both the medial and the lateral horns of the levator muscle tendon are cut through. Then a double armed 5·0 catgut suture is positioned in the middle of the levator muscle. The two ends of this suture are provisionally tied to the upper rim of the tarsal plate. The patient is asked to look straight ahead and the position of the operated eyelid can be compared with the other side. The result should be symmetrical. When an under- or overcorrection is still present, this can be overcome by setting the suture higher or lower in the levator muscle or on the tarsal plate. When the result is satisfactory, two more catgut sutures are added 5 mm medially and laterally from the first one to create an adequate eyelid curve.

Results

This study was carried out on 41 ptosis patients (38 with unilateral ptosis, 3 with bilateral ptosis) operated on since 1982, when the anterior approach levator resection with adjustable sutures was first introduced. The average age of the patients was 31 years (range 2 to 81 years). Sexes were equally distributed in the different groups of diagnoses. Forty-four eyes were treated.

Fig. 1 shows the different causes of ptosis. Fifteen patients had a congenital ptosis, three of them bilaterally, and seven cases were diagnosed as having senile ptosis. Six patients had a traumatic ptosis. Seven patients became ptotic after orbital surgery, while one patient had a ptosis after enucleation. The rest included, among others, cases of Crouzon's disease and oculomotor palsies.

Fig. 2 shows data from 31 out of this group of 44 eyes which were all (44) treated by the anterior approach levator resection with adjustable sutures by one of us (LK) in a uniform and standardised way. The figure shows the levator function of the patients related to the final adjusted amount of resection in mm of the levator muscle. The area between the lines represents the amount of resection as suggested for the levator resection technique.[4] In every case the initial amounts of levator resection were those suggested in the literature.

As can be deduced from Fig. 2, it was almost always necessary to correct the amount of resection. There was no clear-cut relationship between the function of the levator muscle and the amount of resection leading to a cosmetically satisfactory result of the ptosis correction. This group consisted of operations on 31 eyes, two patients having a bilateral congenital ptosis. In these bilateral cases the levator functions were 4/4 and 8/10 mm (right/left lid) respectively and the resections needed were 14/15 and 26/26 mm. Those operations (n=3) which did not lead to a satisfactory postoperative result are indicated by an asterisk. Thirteen operations giving another three unsatisfactory postoperative results

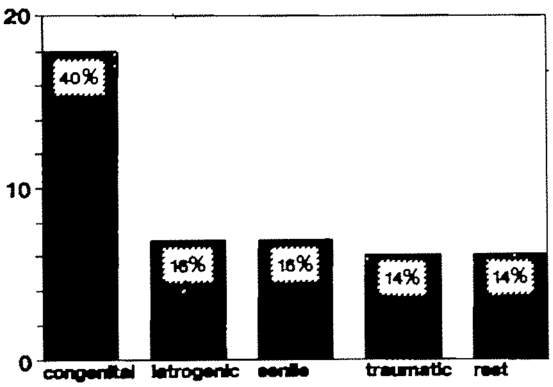

Fig. 1 *Causes of ptosis in 44 eyes treated with the anterior approach levator resection The horizontal axis shows the five subgroups of diagnoses, the abscissa the numbers of eyes in these groups The percentages are indicated in the bars*

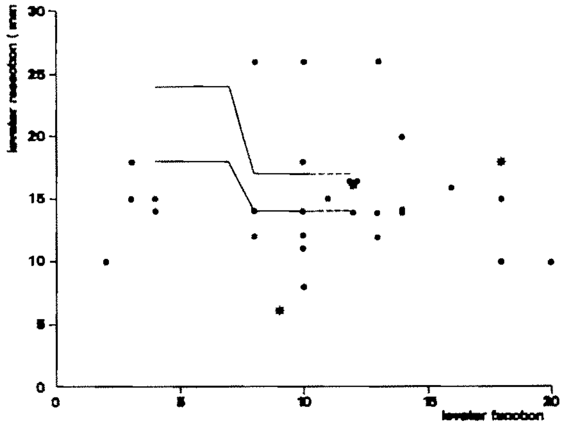

Fig 2 *The preoperative levator function of the ptotic lid related to the actual amount of resection of the levator muscle is shown. The lines represent the upper and lower limits of the amount of resection as proposed by Beard* [4]

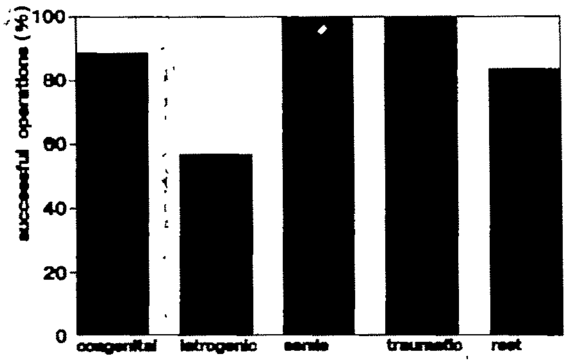

Fig. 3 *Percentages of successful operations in the five groups of diagnoses The horizontal axis shows these five groups, the vertical axis the percentage of successful operations in each group.*

are not shown in this figure owing to failure of preoperative documentation.

As can be seen from Fig. 3 there is a marked difference in the percentages of cosmetically successful operations between the five groups of diagnosis. In the groups consisting of senile and traumatic ptoses all patients had a cosmetically satisfactory eyelid position after the levator resection. In the group of congenital ptosis the percentage of successful operations was about 90%. In cases of iatrogenic ptosis only 55% of the operations led to a good result after one operation. This group was obviously more difficult to treat because we were dealing with ptoses caused by fibrosis and contracted tissues due to surgery and/or radiotherapy. Finally the remaining group contained 80% of cosmetically good postoperative results. The overall success rate of the whole group after a one-step procedure was 86%.

Discussion

The results of a one-step anterior approach levator resection technique with intraoperative adjustable sutures are described in this article. This technique was described before by Simonton and Garber.[6] About 85% of their patients had a cosmetically satisfying eyelid position postoperatively. Making use of a nearly identical technique, they operated on 44 eyes, and of these four eyelids required a revision of the procedure. These authors, however, do not mention data about diagnoses, the amount of resection done, and the pre- and postoperative measurements of their patients. Collin and Tyers[7] treated 55 eyes with ptosis due to an aponeurotic defect, ranging from 1 to 5 mm, making use of a posterior approach levator resection with adjustable sutures.[5] Ten of the 55 eyes (18%) needed a second approach by removal of sutures or stretching of the eyelid. Eventually 81% of the patients showed functional and cosmetically good results.

In our heterogeneous group (in which some of the patients are more difficult to treat than others), treated by an intraoperative monitoring surgical technique, only 14% of the patients had an unsatisfactory eyelid position postoperatively. This relatively good result can be explained by the fact that the anterior approach levator resection with adjustable sutures is a flexible method yielding good results even in difficult conditions. These results support the assumption that in ptosis a number of factors, such as anatomical,[8] neurological, and muscular variations,[5,9] lead to an individual eyelid position. The balance between the strength of the levator muscle and the orbicular muscle may play a major part in the positioning of the eyelid. These hypotheses, however, need further analysis.

The results of this study and data from the literature show that the results of ptosis operations are characterised by unpredictability and the need for individual assessment, not solely by the amount of ptosis and levator function as determined preoperatively.

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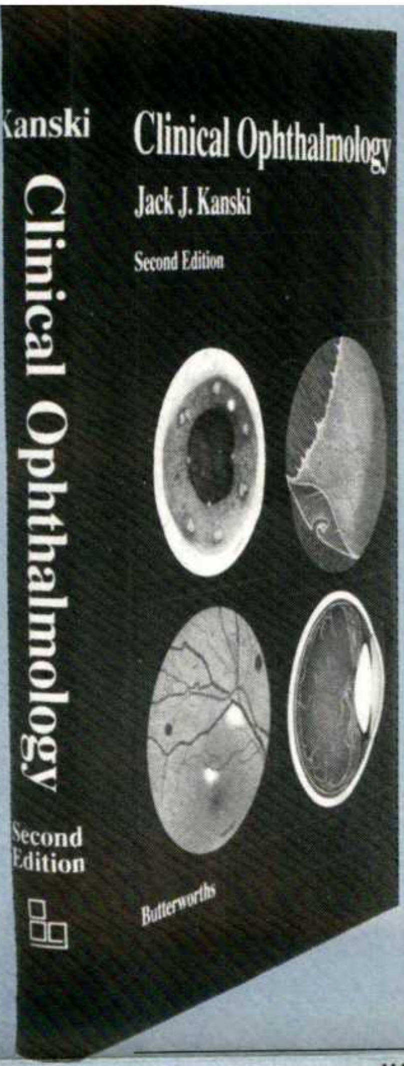

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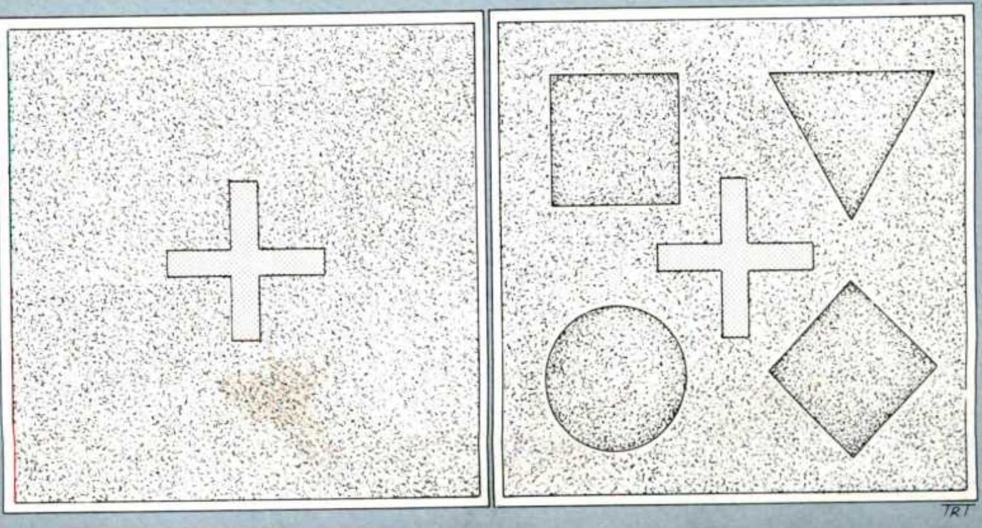

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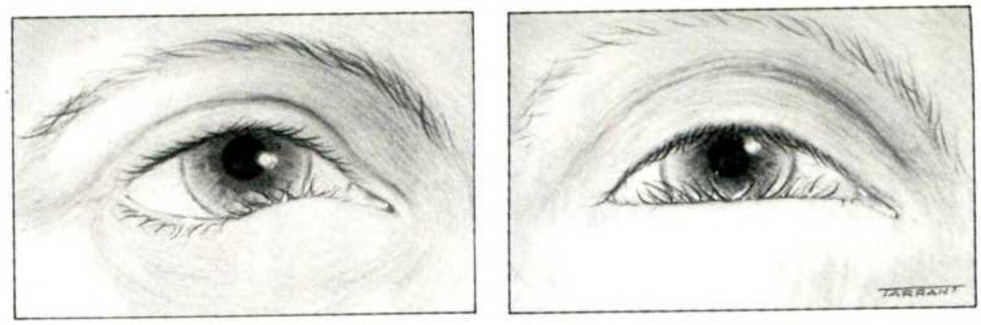

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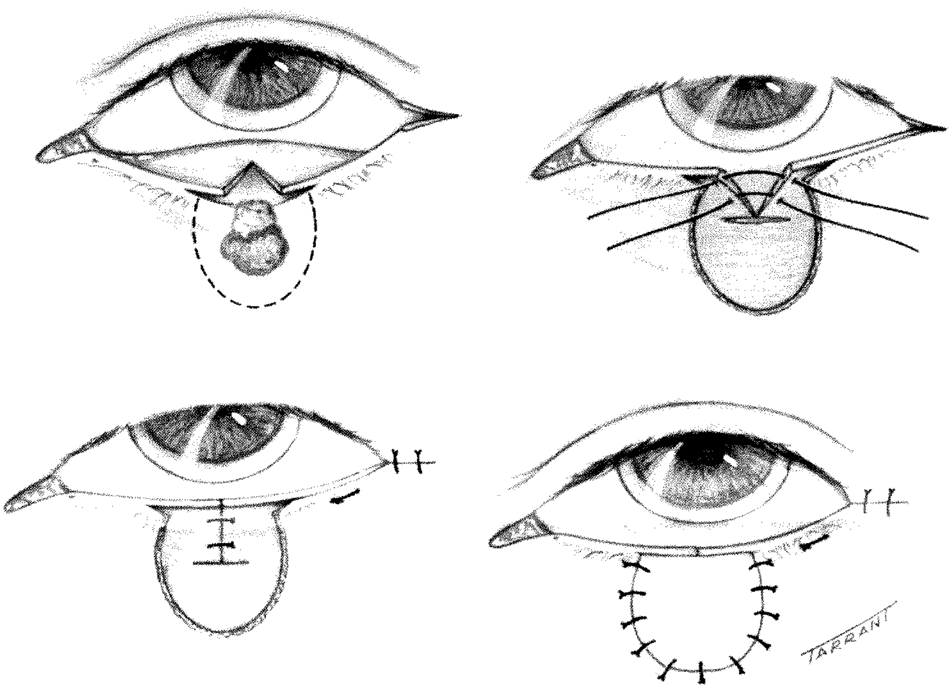

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Michael S Wilson MB BS DO
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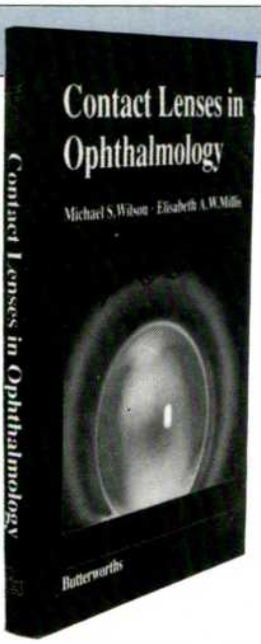

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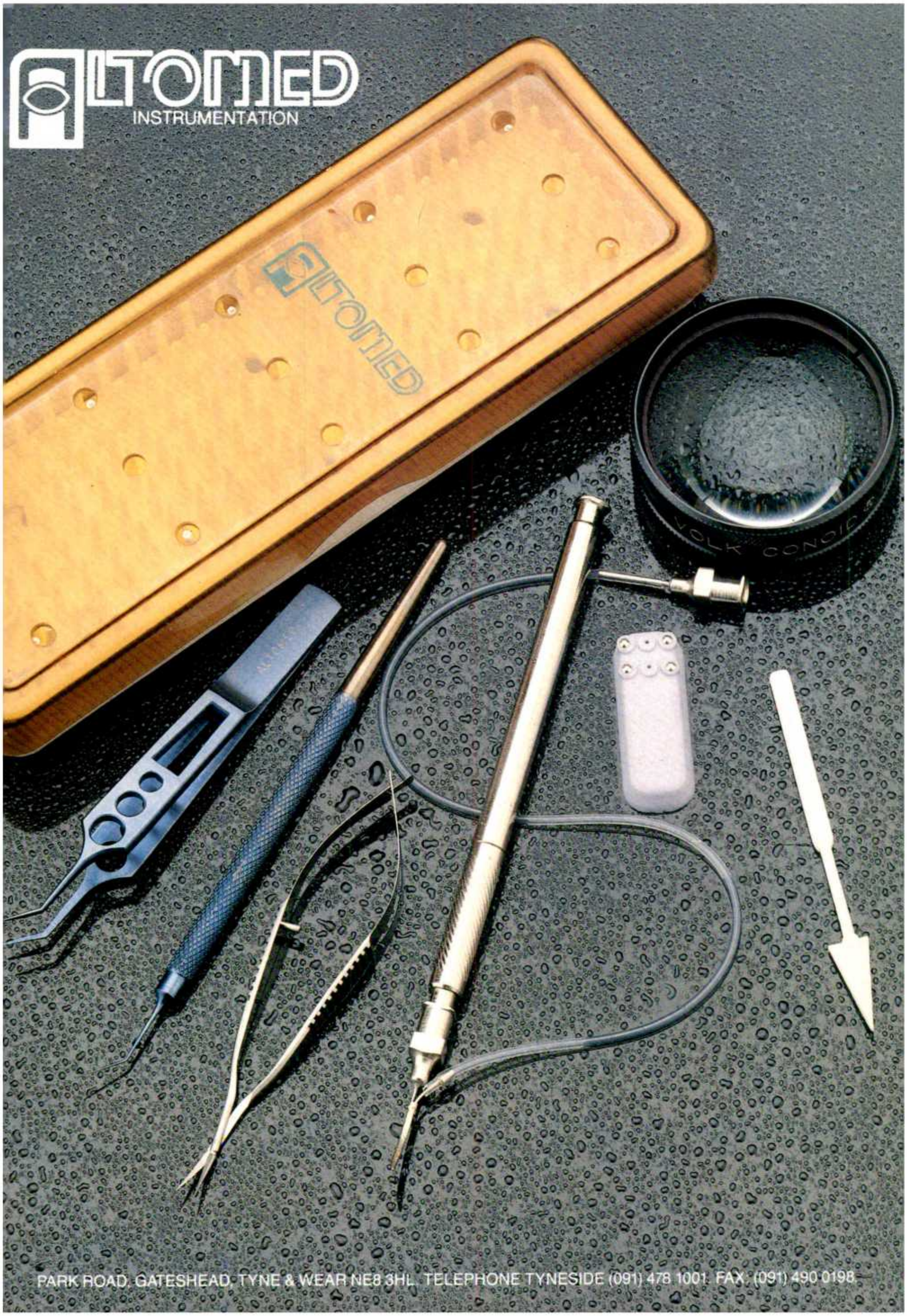

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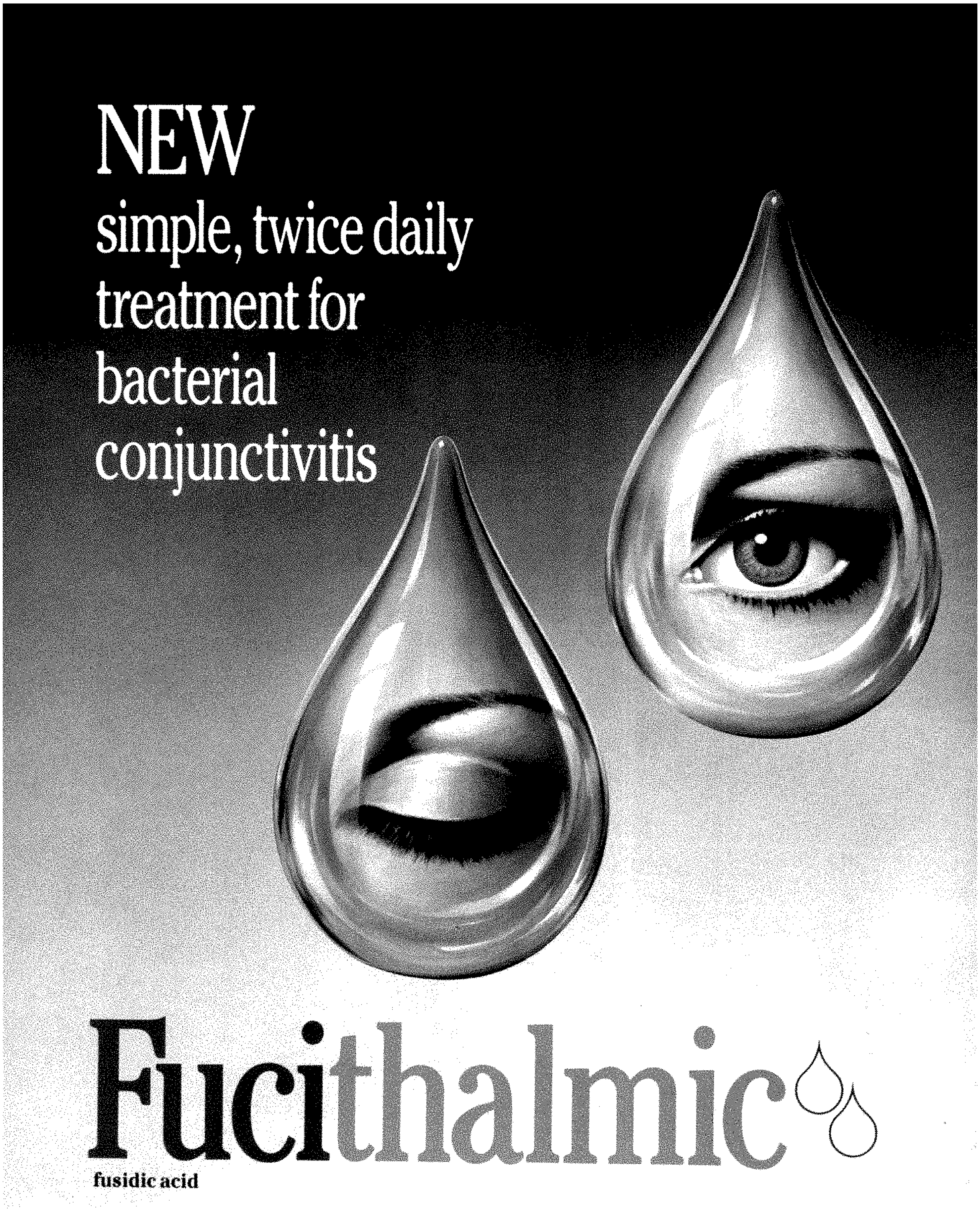
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British Journal of Ophthalmology, 1989, **73**, 419–426

Prostaglandin $F_{2\alpha}$-isopropylester eye drops: effects in normal human eyes*

JORGEN VILLUMSEN AND ALBERT ALM

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SUMMARY The effects of $PGF_{2\alpha}$-isopropylester eye drops on intraocular pressure (IOP) and aqueous humour dynamics were investigated in healthy male volunteers. The other eye was treated with vehicle and used as a control. Special attention was also paid to adverse effects. Single and repeated doses were tested. There was a dose related effect on IOP. Significant reductions were observed 4, 8, and 12 hours after application of 1·0, 2·5, or 10 μg $PGF_{2\alpha}$ equivalents of the drug. With 10 μg the effect lasted 24 hours. An initial tendency towards an increase in IOP was observed for these doses. Repeated doses of 1·0 μg daily or 0·5 μg twice daily produced a significant and lasting IOP reduction of about 2 mmHg for 1-2 weeks. Aqueous humour production was not altered, and outflow facility was not significantly changed. There was a dose dependent hyperaemia with a maximum within 2 hours after application. A foreign body sensation, some pain, and photophobia were noted with increasing doses. A slight miosis of 1 mm was seen in three of six eyes treated with 10 μg. No signs of intraocular inflammation were recorded, but a slight increase in penetration of fluorescein into the anterior chamber was observed after 16 days of treatment.

Prostaglandins have marked effects on the intraocular pressure (IOP). Intracameral injections increase the IOP in rabbits,[1] while low doses of topically applied prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) reduce the IOP in rabbits, cats, and monkeys.[2-7]

The topical application of prostaglandins may also increase the permeability of the blood-aqueous barrier, particularly in rabbits[1 2 3] but also in cats and monkeys.[4-6 8] No systemic side effects have been reported from these studies.

There are only a few studies of the effect of prostaglandins in the human eye. A study of intravenous or intrauterine injections of $PGF_{2\alpha}$ reported a slight IOP reduction following an initial minor increase.[9] The effects on the human eye of a single topical application of 200 μg of the tromethamine salt of $PGF_{2\alpha}$ have been reported.[10] A marked reduction of the IOP was found. Among the reported side effects were ocular pain, conjunctival hyperaemia, and headache, but no aqueous flare or cells in the anterior chamber were seen. The lipid solubility of the tromethamine salt is low, and lipid-soluble esters of $PGF_{2\alpha}$ penetrate the cornea better and can be used in lower doses.[11]

We have evaluated the effects in the human eye of one such lipid soluble ester, $PGF_{2\alpha}$-isopropylester.[12] We found a dose dependent reduction in IOP without a concomitant reduction in aqueous flow or increase in outflow facility. The drug also produced a dose dependent conjunctival/episcleral hyperaemia and ocular external irritation, mainly in the form of a foreign body sensation.

Material and methods

STUDY DESIGN

$PGF_{2\alpha}$-isopropylester produces some foreign body sensation and conjunctival hyperaemia even in low doses, which prevented a reliable masking of the study. Thus all trials reported here were designed as unmasked, open studies but in which the IOP readings were made in a masked fashion. All participants were healthy male volunteers between 22 and 45 years of age. They did not receive any other topical or systemic drug during the studies. Some of the subjects participated in two of the trials. The study protocols were reviewed and approved by the National Board of Health and Welfare and by the Ethics Committee of the Medical Faculty, University of Umeå. A signed informed consent was obtained from each participant.

A. In a dose finding study IOP response and side effects were determined for 0·1, 0·5, 2·5, and 10 μg

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Correspondence to Dr J Villumsen

*Presented at the 7th International Congress of Eye Research held in Nagoya 25 September – 1 October 1986, and at the International Symposium on Prostaglandins and Related Compounds in Ophthalmology held in Tokyo 2–3 October 1986

$PGF_{2\alpha}$ administered as isopropylester in eye drops. Six subjects participated. The eye to be treated was randomly selected and a 25 µl eye drop was applied in the conjunctival sac at 8 am (T=0). Randomisation was carried out only once and the same eye was used for all four doses. The other eye was treated with the vehicle. The IOP was determined before treatment and at T=0·5, 1, 2, 4, 8, 12, and 24 hours. At each examination the eyes were evaluated for conjunctival hyperaemia and aqueous flare and cells. Corneal sensitivity was estimated with an aesthaesiometer (Luneau and Coffignon, Paris) 90 minutes after application of the eye drops, and the diameter of the pupils was determined on a Goldmann perimeter under standard light conditions (31·5 apostilbs) 30 minutes later. The treatment schedule started with the lowest dose, and then successively higher concentrations were tested with a washout period of at least 48 hours between doses.

B. Six subjects were treated with 1·0 µg $PGF_{2\alpha}$-isopropylester at 8 am (T=0) for six days in one randomly selected eye. The other eye was treated with vehicle. Corneal sensitivity and pupil diameters were not examined in this study, but the eyes were examined and IOP determined before treatment and at T=0·5, 2, 4, 8, 12, and 24 hours on days 1, 3, and 5. On the sixth day the blood-aqueous barrier permeability was estimated by fluorophotometry.

C. Ten subjects were treated according to the same protocol as in study B with the exception that the dose was divided into two doses of 0·5 µg $PGF_{2\alpha}$-isopropylester given at 8 am (T=0) and 8 pm (T=12), and given for 16 days. The IOP was determined and the eyes were examined before application of the morning dose and at T=4, 8, 12, and 24 hours on days 1, 8, and 15. On day 10 the aqueous humour production was determined in both eyes. Blood-aqueous barrier permeability was determined on day 16 and about two months later.

D. Sixteen subjects were given 1·0 µg $PGF_{2\alpha}$ in one randomly selected eye and vehicle in the other eye. Five hours later the IOP and outflow facility were determined.

AQUEOUS HUMOUR DYNAMICS

The IOP was determined with a Goldmann tonometer. Five consecutive readings were done in each eye, the right eye being taken first. The scale of the tonometer was masked to the examiner. The highest and lowest values were discarded, and the mean of the remaining three values was accepted as the true IOP. The tonometer prism was cleaned between readings in the right and left eye to avoid drug contamination.

Aqueous flow was determined by fluorophotometry (Fluorotron Master). Three drops of 2% sodium fluorescein was applied at 5-minute intervals. Measurements were done hourly 5 to 10 hours later, and from these data the aqueous flow was calculated.[13] The outflow facility was calculated from 4-minute tonograms performed with a pneumatonometer (Alcon, Fort Worth) with the 10 g weight.

SIDE EFFECTS

Hyperaemia was evaluated from photographs of the exterior of the two eyes. Pictures of the temporal conjunctiva were projected on to a screen with an overall magnification of approximately ×25. On the screen a square of 14×14 dots, 1·5 mm in diameter, was placed, with an interval of 1 cm between dots. All dots having some contact with a vessel were counted (Fig. 1). The evaluation of the photographs was masked. The difference between counts in the $PGF_{2\alpha}$ treated eye and the vehicle treated eye was used as an estimate of the drug induced hyperaemia. Fluorophotometry was used to estimate the blood-aqueous barrier permeability.

Corneal and aqueous fluorescein concentrations were determined in the two eyes 2, 4, 6, and 8 hours after an oral dose of 400–500 mg sodium-fluorescein diluted in orange juice. Subjective side effects were registered after each dose in A and after each day of IOP measurements in B and C. Visual disturbances, foreign body sensation, itching, pain, photophobia or any systemic symptom were asked for. The side effects were graded absent, slight, moderate, or severe and the duration was recorded.

STATISTICAL EVALUATION

The two-tailed Student's t-test of paired data was used to calculate observed differences. The results are presented as mean (with SEM). Drug effects were based on the difference in IOP between the two eyes. We assume that a possible, centrally mediated effect on IOP, induced by the experimental procedures, would affect the two eyes similarly. Furthermore, prostaglandins are rapidly inactivated in the lungs,[14] and an effect on the contralateral eye induced by systemically absorbed $PGF_{2\alpha}$ seems unlikely.

Results

AQUEOUS HUMOUR DYNAMICS

The effects on the IOP are presented in Tables 1–3. These tables include only the initial IOPs and values obtained at times where a significant effect was seen with at least one dose (study A) or on some day (studies B and C). Remaining non-significant differences are included in Fig. 2, which provides a summary of the observed differences between the two eyes for the three studies A–C. In the dose-response study (A) 0·1 µg and 0·5 µg $PGF_{2\alpha}$ had no

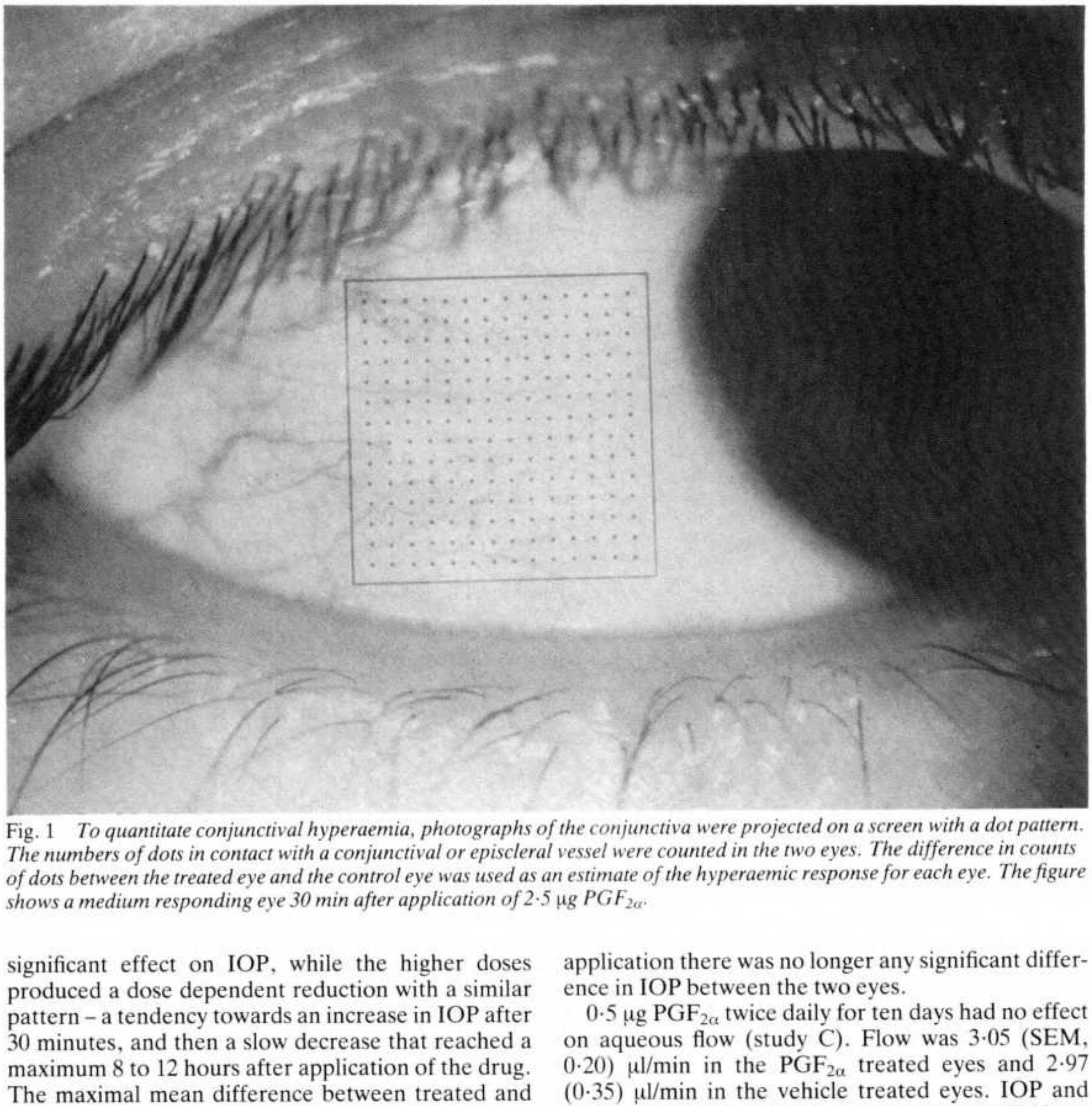

Fig. 1 *To quantitate conjunctival hyperaemia, photographs of the conjunctiva were projected on a screen with a dot pattern. The numbers of dots in contact with a conjunctival or episcleral vessel were counted in the two eyes. The difference in counts of dots between the treated eye and the control eye was used as an estimate of the hyperaemic response for each eye. The figure shows a medium responding eye 30 min after application of 2·5 μg $PGF_{2\alpha}$.*

significant effect on IOP, while the higher doses produced a dose dependent reduction with a similar pattern – a tendency towards an increase in IOP after 30 minutes, and then a slow decrease that reached a maximum 8 to 12 hours after application of the drug. The maximal mean difference between treated and non-treated eyes was 5·7 mmHg observed eight hours after application of 10 μg $PGF_{2\alpha}$. An effect that lasted 24 hours was observed only with the 10 μg dose.

With 1·0 μg given once daily for six days (study B) a significant IOP reduction of 2-3 mmHg was observed four to eight hours after application of the drug throughout the study. No 24-hour effect was obtained, and there was no tendency to an increase or decrease of the response. With repeated doses of 0·5 μg twice daily for 16 days (study C) a significant reduction in IOP of about 2 mmHg was obtained. The IOP was measured after conclusion of the study every twelfth hour, and 36 hours after the last drug application there was no longer any significant difference in IOP between the two eyes.

0·5 μg $PGF_{2\alpha}$ twice daily for ten days had no effect on aqueous flow (study C). Flow was 3·05 (SEM, 0·20) μl/min in the $PGF_{2\alpha}$ treated eyes and 2·97 (0·35) μl/min in the vehicle treated eyes. IOP and outflow facility (study D) are presented in Table 4. There was a significant reduction in IOP in the eyes treated with 1·0 μg $PGF_{2\alpha}$ when compared with the vehicle treated eyes, but no significant change in outflow facility.

SIDE EFFECTS

The hyperaemic response for the dose response study is presented in Fig. 3. A dose dependent hyperaemia was seen about 10 minutes after application of the drug. 0·1 and 0·5 μg $PGF_{2\alpha}$ produced a slight hyperaemia for about one hour. The hyperaemia after 2·5 or 10 μg was equally pronounced but more prolonged with 10 μg. The hyperaemia involved

Table 1 *Intraocular pressures in treated and untreated eyes at various times after application of 0·1, 0·5, 2·5, or 10 μg $PGF_{2\alpha}$-isopropylester in study A. The values are mean with SEM (n=6). Statistical significances were calculated for the paired differences*

T h	*Vehicle*	*$PGF_{2\alpha}$*	*Difference*	*p<*
0·1 μg				
0	15·7 (1·1)	15·4 (1·1)	0·3 (1·0)	
4	13·9 (0·7)	12·7 (1·1)	1·2 (0·9)	
8	15·4 (1·0)	13·5 (1·3)	1·9 (1·1)	
12	14·6 (1·0)	14·3 (1·4)	0·3 (1·0)	
24	13·0 (1·1)	12·2 (1·3)	0·7 (0·5)	
0·5 μg				
0	14·4 (1·1)	12·8 (1·2)	1·6 (0·9)	
4	14·8 (1·2)	12·9 (1·5)	1·9 (0·9)	
8	14·4 (1·2)	13·5 (1·4)	0·9 (0·8)	
12	13·6 (1·5)	11·9 (1·5)	1·7 (0·9)	
24	14·9 (1·5)	14·2 (1·4)	0·7 (0·5)	
2·5 μg				
0	14·1 (1·4)	12·3 (1·3)	1·8 (0·8)	
4	13·2 (1·3)	11·4 (1·0)	1·8 (0·6)	0·05
8	15·0 (1·8)	11·8 (1·1)	3·3 (0·9)	0·025
12	14·8 (1·5)	11·5 (1·1)	3·3 (1·2)	0·05
24	13·7 (1·4)	12·8 (1·5)	0·8 (0·7)	
10 μg				
0	14·0 (1·2)	13·2 (1·1)	0·8 (0·5)	
4	13·5 (1·7)	11·2 (1·3)	2·3 (0·8)	0·05
8	16·1 (1·1)	10·4 (1·4)	5·7 (1·4)	0·025
12	13·9 (1·3)	9·6 (0·9)	4·3 (0·9)	0·005
24	14·5 (1·3)	12·2 (1·3)	2·3 (0·3)	0·005

Table 2 *Intraocular pressures in treated and untreated eyes at various times after application of 1·0 μg $PGF_{2\alpha}$-isopropylester once daily for six days in study B. Mean with SEM (n=6). Statistical significances were calculated for the paired differences*

T h	*Vehicle*	*$PGF_{2\alpha}$*	*Difference*	*p<*
Day 1				
0	15·6 (1·7)	15·4 (1·6)	0·2 (0·8)	
2	15·1 (1·1)	13·6 (1·1)	1·5 (0·9)	
4	14·7 (0·8)	11·8 (1·2)	2·9 (0·6)	0·01
8	15·5 (1·4)	12·5 (1·6)	3·0 (0·8)	0·025
12	15·3 (1·3)	13·0 (1·3)	2·3 (1·2)	
24	14·3 (1·4)	13·1 (1·5)	1·2 (0·8)	
Day 3				
0	13·4 (1·3)	12·7 (1·6)	0·7 (0·7)	
2	14·9 (0·9)	13·3 (1·2)	1·6 (0·5)	0·025
4	15·2 (1·3)	12·7 (1·3)	2·4 (1·0)	
8	15·6 (1·4)	12·4 (1·3)	3·2 (1·2)	0·05
12	15·5 (1·5)	12·3 (0·9)	3·2 (1·0)	0·05
24	13·0 (1·3)	13·2 (1·5)	−0·2 (0·8)	
Day 5				
0	13·8 (1·2)	13·7 (1·3)	0·2 (0·4)	
2	14·5 (1·1)	13·2 (0·8)	1·3 (0·3)	0·025
4	14·9 (1·6)	12·5 (1·0)	2·4 (0·8)	0·05
8	13·9 (1·6)	11·0 (1·0)	2·9 (0·9)	0·025
12	13·2 (1·1)	12·2 (1·1)	1·0 (0·8)	
24	12·2 (1·4)	11·8 (1·4)	0·3 (0·5)	

Table 3 *Intraocular pressures in treated and untreated eyes at various times after application of 0·5 μg $PGF_{2\alpha}$-isopropylester twice daily for 16 days in study C. Mean with SEM (n=10). Statistical significances were calculated for the paired differences*

T h	*Vehicle*	*$PGF_{2\alpha}$*	*Difference*	*p<*
Day 1				
0	15·2 (1·0)	14·9 (0·7)	0·3 (0·4)	
4	15·3 (0·9)	13·1 (0·6)	2·2 (0·9)	0·05
8	14·8 (0·9)	13·3 (0·8)	1·6 (0·8)	
12	14·8 (0·8)	13·1 (0·8)	1·6 (0·7)	0·05
24	13·2 (0·9)	12·2 (0·7)	1·0 (0·5)	
Day 8				
0	13·7 (0·8)	12·0 (0·7)	1·7 (0·6)	0·025
2	14·3 (0·7)	11·8 (0·6)	2·5 (0·5)	0·001
4	14·0 (0·6)	11·5 (0·5)	2·5 (0·4)	0·001
8	13·6 (0·7)	11·8 (0·6)	1·8 (0·3)	0·001
12	13·5 (0·9)	11·4 (0·8)	2·1 (0·4)	0·001
24				
Day 15				
0	13·7 (0·8)	12·7 (0·6)	1·0 (0·4)	0·05
4	14·1 (0·8)	11·9 (0·5)	2·1 (0·5)	0·005
8	13·6 (0·8)	12·0 (0·6)	1·6 (0·4)	0·005
12	13·4 (0·7)	12·1 (0·7)	1·3 (0·3)	0·005
24	13·7 (0·8)	12·3 (0·8)	1·3 (0·5)	0·025

episcleral vessels as well as conjunctival vessels. The response to 1·0 μg once daily (study B) was more pronounced than previously found for 0·5 μg, but clearly less than the 2·5 μg response. It was the same on day 5 as on day 1. Even 0·5 μg×2 (study C) produced a slight hyperaemia, but it had vanished at the time of ocular examination four hours later.

No cells or flare were found in any of the studies. Fluorescein concentrations in the cornea and aqueous ranged between 42 and 328 ng/ml and 7 and 112 ng/ml respectively, two to eight hours after an oral dose of 400–500 g sodium fluorescein in studies B and C. The concentrations in the cornea were, as a rule two to three times that in the aqueous. The ratio of treated eye to untreated eye was calculated for both cornea and aqueous, and the results are presented in Table 5. Generally the fluorescein concentrations in the treated eyes tended to be lower than in the untreated eyes in study B while the opposite was true for study C. The participants in study C were reexamined two months later. At that time no difference was observed between the two eyes for either cornea or aqueous.

No effect on the pupil diameter could be shown for doses up to 2·5 μg $PGF_{2\alpha}$. 10 μg produced a miosis of 1 mm in three of six participants. No change in corneal sensitivity was observed. The subjective adverse effects showed a marked dose dependence. No discomfort was noted for 0·1 μg. 0·5 μg produced a minor foreign body sensation in the treated eye in three of the seven participants for about one hour.

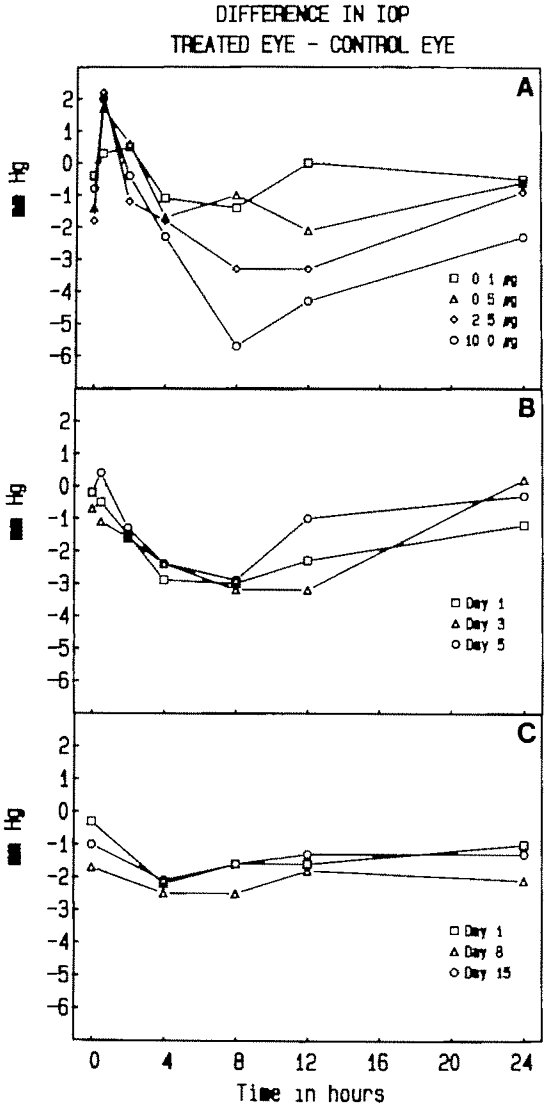

Fig. 2 *The mean difference (IOP in control eye minus IOP in treated eye) at various times after application of drugs.* Top: *Single doses of four different doses of $PGF_{2\alpha}$ (study A)* Middle. *Repeated doses of 1·0 µg $PGF_{2\alpha}$ once daily for 6 days (study B).* Bottom· *Repeated doses of 0·5 µg $PGF_{2\alpha}$ twice daily for 16 days (study C)*

After 2·5 µg discomfort was noted by all participants for two to three hours. In the treated eye a marked foreign body sensation was felt by three subjects, and the remaining three had an experience of pain for about the same time. 10 µg produced photophobia and pain in the treated eyes of all six participants, one having a foreign body sensation for 12 hours. The side effects noted by the participants receiving 1·0 µg daily for six days were regarded as mild by everyone and remained unchanged during the study. A foreign body sensation was noted about 15 minutes after application of the drug and lasted about two hours. With 0·5 µg twice daily a slight discomfort for about one hour was experienced by only two of 10 persons on the first day of treatment. On days 8 and 15, however, discomfort was felt for one to two hours in the $PGF_{2\alpha}$ treated eyes of nine of 10 participants. No discomfort was recorded from the vehicle treated eyes in any of the studies.

Table 4 *Intraocular pressures in mmHg and outflow facilities in µl/min/mmHg in treated and untreated eyes five hours after 1·0 µg $PGF_{2\alpha}$ (study D). Mean with SEM (n=16) Statistical significances were calculated for the paired differences*

	IOP	*Facility*
Control eye	17·0 (0·6)	0·311 (0·029)
Treated eye	15·3 (0·7)	0·334 (0·033)
Difference	1·7 (0·4)	0·024 (0·029)
p<	0·005	NS

Discussion

The purpose of study A was to find a suitable dose for further tests. Without previous knowledge of the effects on the eye we chose to use increasing concentrations of $PGF_{2\alpha}$ in the same eye. The study served its purpose, but an unexpected observation was the difference in IOP between the two eyes observed even before application of the three higher doses (Table 1). A similar difference in pretreatment IOP was not observed before 0·1 µg $PGF_{2\alpha}$ or before any of the other studies. 0·1 µg $PGF_{2\alpha}$ had no effect on IOP for the first 24 hours, and the likelihood that it caused a slow and almost significant ($p<0·1$) reduction 48 hours later seems remote. Thus we have to assume that this is due to random variation. The information obtained from study A enabled us to choose a dose for further studies, but the magnitude of the effect with higher doses of $PGF_{2\alpha}$-isopropylester may be exaggerated by the unexplained difference in pretreatment IOP between the two eyes. Moreover the IOP of the vehicle treated eyes tended to become lower during studies A–C. Obviously we cannot rule out a contralateral effect, but a likely alternative is that the participants become more relaxed as they become more familiar with the examination procedures. We could find no tendency to a reduction in IOP due to the five rapid measurements on each examination.

The IOP response in the human eye seems to follow the pattern seen in primate eyes, where a

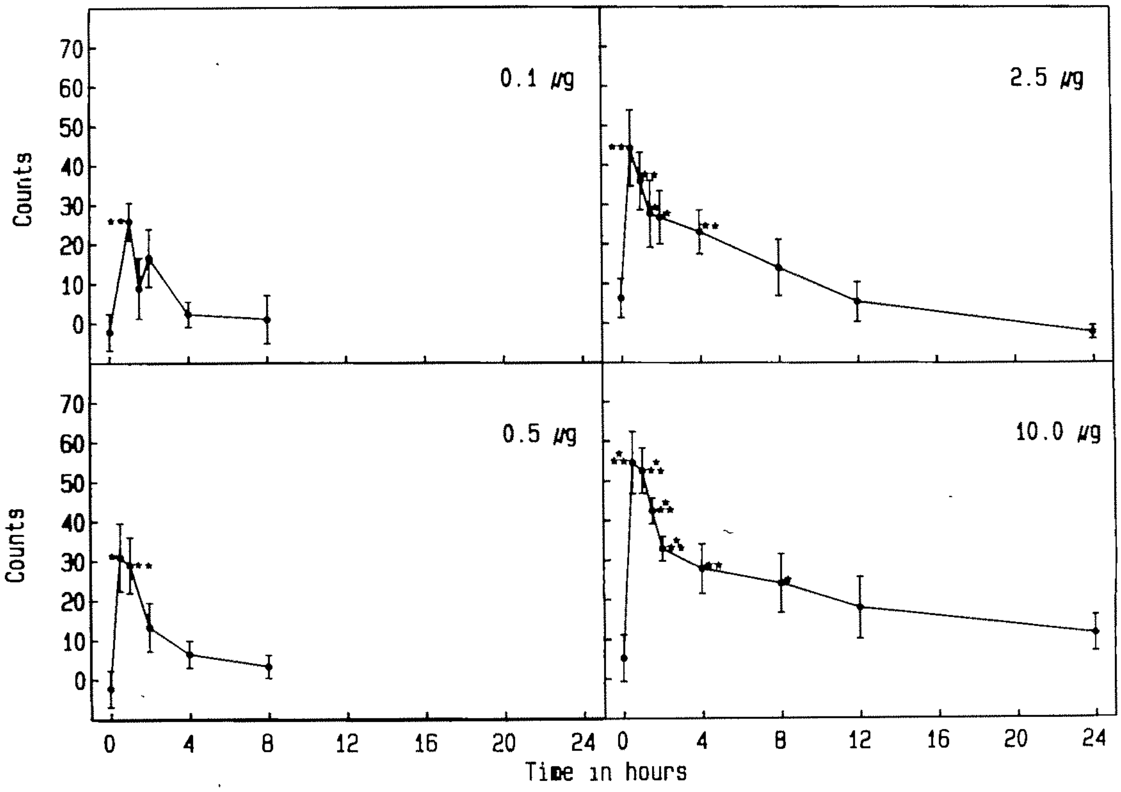

Fig. 3 *Difference in hyperaemia: treated eye minus control eye The hyperaemic response (see Fig. 1) at various times after application of 0·1, 0·5, 2·5, or 10 μg PGF$_{2\alpha}$ (study A). Since no difference could be observed between the two eyes after eight hours with 0·1 and 0·5 μg, no more photographs were taken. The values are mean with SEM p Values are indicated by asterisks: * p<0·05. ** p<0·01. ***p<0·001.*

Table 5 *The ratio (treated eye/untreated eye) for fluorescein concentration in cornea and aqueous 2–8 hours after an oral dose of 400–500 mg sodium fluorescein. In study B six subjects had been treated with 1·0 μg PGF$_{2\alpha}$-isopropylester once daily for six days in one eye, and in study C 10 subjects had been treated with 0·5 μg PGF$_{2\alpha}$-isopropylester twice daily for 16 days in one eye Values are mean with SEM Significance levels indicate the probability that the true ratio is 1·0*

T h	*Cornea*	*p<*	*Aqueous*	*p<*
Study B				
2	0·78 (0·05)	0·01	0 95 (0 03)	NS
4	0·84 (0 05)	0·025	0 92 (0·04)	NS
6	0·86 (0 04)	0 01	0 91 (0·04)	NS
8	0·86 (0 05)	0·05	0 97 (0·07)	NS
Study C				
2	1·29 (0·12)	0·05	1 08 (0 03)	0 025
4	1·17 (0 06)	0·025	1 08 (0·03)	0·025
6	1·13 (0·06)	NS	1 02 (0·03)	NS
8	1 06 (0 04)	NS	1 03 (0·05)	NS

biphasic IOP response is found.[3-5] The initial increase in IOP observed in the dose-finding study (Fig. 2) was not statistically significant but occurred with all four doses. The reduction in IOP is slow in comparison with that from commonly used glaucoma drugs. There is no difference between the tromethamine salt, as reported by Guiffré,[14] and the isopropylester of PGF$_{2\alpha}$ with regard to time of onset. Both have an effect from about four hours, with a maximum 8-12 hours after application. The doses of the isopropylester of PGF$_{2\alpha}$ used here are all less than 5% of the dose of tromethamine salt previously used in human eyes.[16] Increased lipid solubility of PGF$_{2\alpha}$ thus reduces the total dose needed for IOP reduction.

Our results did not clarify the mechanism behind the IOP reduction. No change in aqueous humour production was found, and a recent study reported a similar lack of effect of PGF$_{2\alpha}$ on aqueous flow in humans.[15] No increase in outflow facility was found in study D. There is, however, a possibility that PGF$_{2\alpha}$

affects neither aqueous flow nor outflow facility. In monkeys $PGF_{2\alpha}$ reduces IOP without reducing aqueous flow[5 7] or increasing outflow facility.[16] Recent studies indicate that the IOP reduction in monkeys is due to an increased uveoscleral outflow.[17 18] Uveoscleral outflow is present in human eyes,[19] and an increase in uveoscleral outflow could well be part of the mechanism in the human eye.

SIDE EFFECTS

In doses that reduced the IOP $PGF_{2\alpha}$ also produced local irritation, mainly in the form of a foreign body sensation and, in higher doses, pain and photophobia. This sensation appeared first after one or two minutes, unlike the immediate stinging sensation experienced with physically irritating eye drops. We conclude that this is a pharmacologically mediated pain response. Prostaglandins produce hyperalgesia rather than pain and exert their effect synergistically with pain producing mediators such as bradykinin and histamine.[20] When 0·5 μg $PGF_{2\alpha}$ was given twice daily for two weeks there was a tendency towards increasing discomfort during the study. Although the discomfort was mild even at the end of the study, this observation suggests that side effects may increase with repeated treatment.

Prostaglandins are involved in various aspects of the inflammatory response of the eye. They seem to produce miosis during surgery,[21] which may explain the slight miosis observed in three participants after 10 μg $PGF_{2\alpha}$. They mediate inflammatory vasodilatation[22] and increase blood flow through the anterior uvea in rabbits.[23] Flare and cells have been observed in the anterior chamber of experimental animals after topical application of $PGF_{2\alpha}$.[2 4 5 7] The human eye seems to be less sensitive in this respect, since no cells or aqueous flare were observed. The fluorophotometry results indicated an increased permeability of the barrier in study C but not in study B. Sodium fluorescein is a small molecule which makes this a potentially very sensitive technique. Entrance of fluorescein into the anterior chamber from limbal vessels, with the cornea as a reservoir, is a possible source of error. This seems to be an important route in rabbits.[24] If this is true also for human eyes, the slight increase in anterior chamber fluorescence observed in study C may only reflect a corresponding difference for the cornea (see Table 5), rather than increased penetration through the blood-aqueous barrier. In study B the opposite occurred; ratios lower than 1·0 were observed for both cornea and aqueous. Further studies are obviously necessary to resolve this question.

The use of very low doses of $PGF_{2\alpha}$, made possible with the increased lipid solubility of the ester, did not cause a sufficiently efficient separation of effect and subjective side effects. However, the results indicate that prostaglandins are potentially effective for IOP reductions and that the mechanism behind the IOP reduction may differ from commonly used glaucoma drugs. It seems worthwhile to evaluate other formulations of the drug or other prostaglandins, with respect also to long-term effects on the IOP and the blood-aqueous barrier.

$PGF_{2\alpha}$-isopropylester eye drops were supplied by Pharmacia Ophthalmics AB, Uppsala, Sweden The authors have no commercial or proprietary interest in $PGF_{2\alpha}$ eye drops

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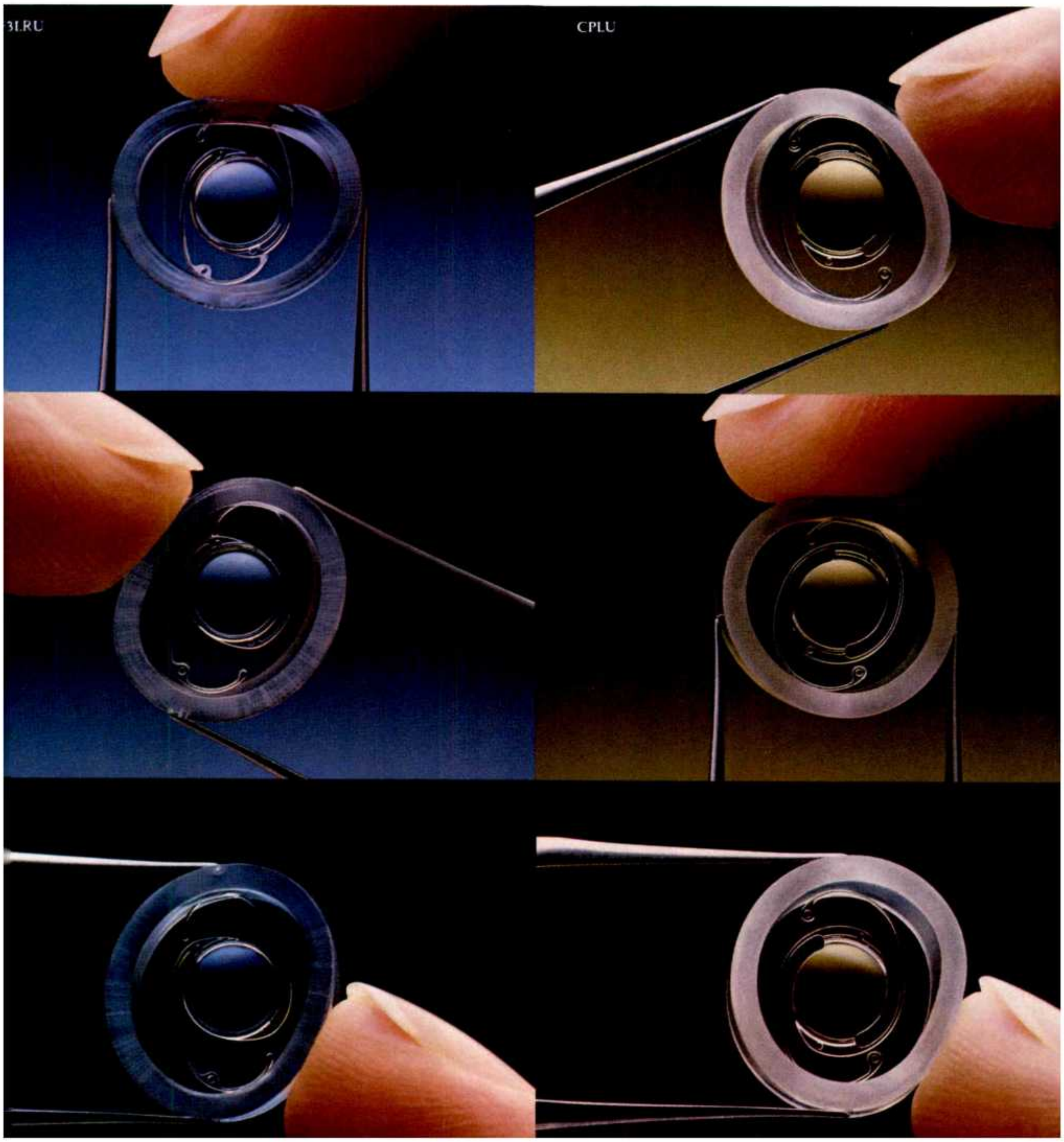

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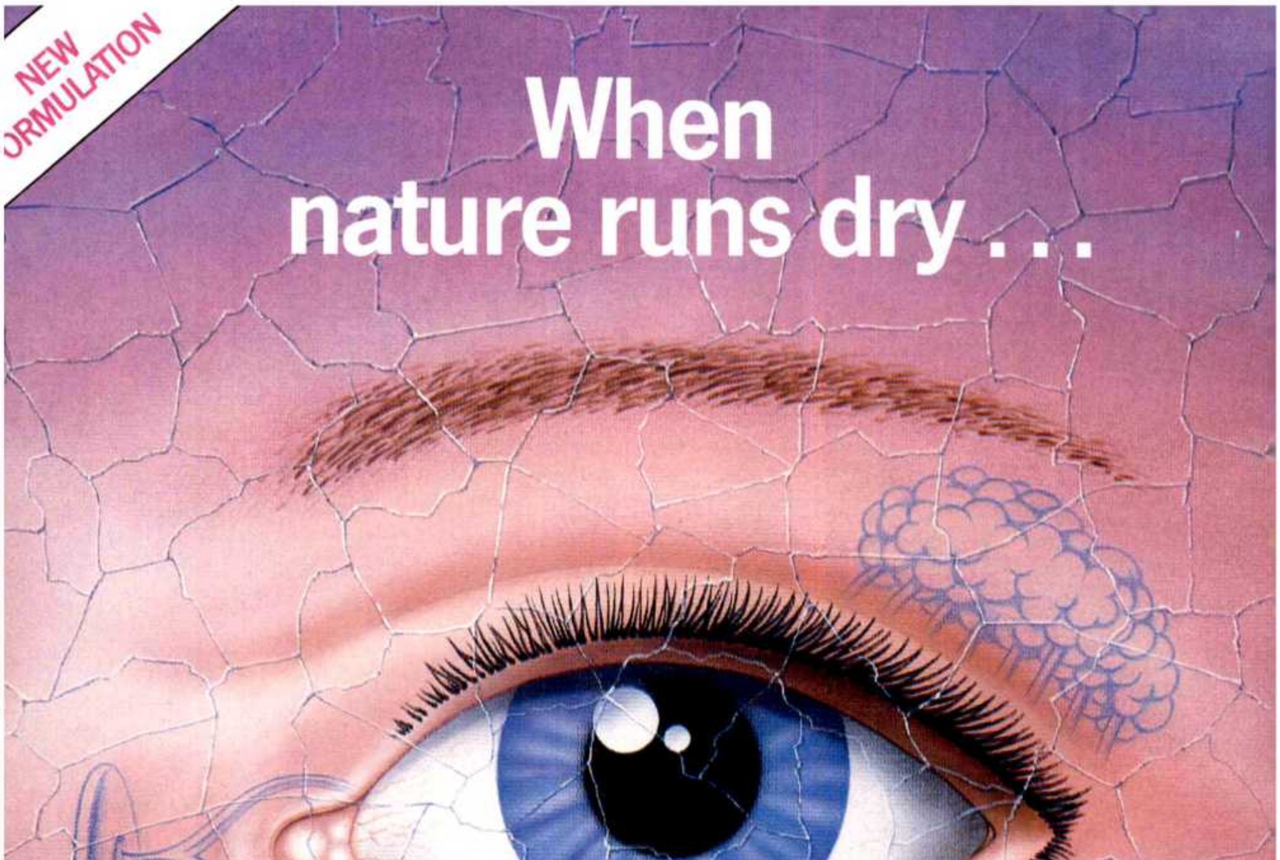
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Ocular complications in homocystinuria—early and late treated*

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SUMMARY Homocystinuria due to cystathionine-β-synthetase deficiency is an autosomal recessive disorder of methionine metabolism with an incidence in Ireland of 1 in 52 544 births. Ocular complications in untreated patients include ectopia lentis, secondary glaucoma, optic atrophy, and retinal detachment. There are no characteristic signs or symptoms in infancy, and early detection relies on screening of newborn babies. Nineteen patients with homocystinuria were studied; 14 received dietary treatment and vitamin supplementation starting in the newborn period. Of these, none developed ectopia lentis after a mean follow-up of 8·2 years, compared with a 70% dislocation rate in untreated patients with a similar follow-up period. Ectopia lentis developed and progressed in five patients diagnosed later in life, despite tight biochemical control. The risk of ocular complications in homocystinuria can be substantially reduced in patients started on treatment within six weeks of birth.

Homocystinuria due to cystathionine-β-synthetase deficiency is the second most common inborn error of amino acid metabolism. It is an autosomal recessive disorder of methionine metabolism first described in 1962.[1,2] Plasma homocysteine is increased, chiefly as the disulphide homocystine (homocysteine-homocysteine), and spills into the urine.[3] Plasma methionine is likewise increased and plasma cysteine and cystine are decreased. Two disorders of cystathionine-β-synthetase exist; both produce the same amino acid abnormalities and clinical features. One form responds to pharmacological doses of pyridoxine (vitamin B_6), the other more common and more severe form is pyridoxine-unresponsive and requires a low-methionine diet supplemented with cystine.

The incidence of homocystinuria in Ireland is 1 in 52 544 newborns screened (Cahalane S, personal communication). Not all countries or regions within countries screen for this disorder because of its variable, geographical incidence, which is as rare as 1 in 573 000 newborns in some European countries.[4]

Untreated patients have ectopia-lentis, mental retardation, skeletal disorders and thromboembolic episodes[3] which can lead to death by 20 years of age. The major ocular complication is ectopia lentis, which probably occurs in up to 70% of patients by 8 years of age and in more than 95% by 40 years.[5] We describe the ocular findings in 19 patients with homocystinuria due to cystathionine-β-synthetase deficiency and correlate these findings with the age at commencement of treatment and biochemical control.

Patients and methods

Nineteen patients with homocystinuria were studied. There were 10 males and nine females, aged 4·4 to 17·3 years. Fourteen patients were detected by screening (group 1; Table 1) and were on treatment from the first six weeks of life, while five patients began treatment in childhood (group 2; Table 2). The Guthrie microbiological inhibition assay for methionine was used for screening, performed on a dried blood spot between the third and sixth days of

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life. The diagnosis was confirmed by the demonstration of increased plasma homocyst(e)ine (homocystine plus homocysteine) and methionine and decreased plasma cyst(e)ine (cystine plus cysteine).[3] Cystathionine-β-synthetase activity was assayed in cultured skin fibroblasts of seven randomly chosen patients (Tables 1 and 2). The pyridoxine status of all patients was determined.

All patients attend the Inherited Metabolic Unit. One patient (case 17) responded to pyridoxine and folate supplements. The remainder required a low-methionine diet supplemented with cystine. The diet was monitored and adjusted in accordance with monthly or bimonthly measurement of plasma methionine, homocyst(e)ine, and cyst(e)ine.[4] Pyridoxine supplementation was reinstituted in all pyridoxine-unresponsive patients (14 of 17 cases) on the theoretical assumption that some residual enzyme activity might be stimulated, enabling more methionine to be tolerated. Biochemical control was defined as good if homocyst(e)ine levels were <10 μm/l, fair 10–15 μm/l, and poor if >15 μm/l. We also classified control for cyst(e)ine as good if >22 μm/l, fair 12–21 μm/l, and poor <12 μm/l.

Each patient underwent a detailed ophthalmic examination which included testing of visual acuity, motility assessment, cycloplegic retinoscopy, slit-lamp biomicroscopy, and direct and indirect ophthalmoscopy. Historical information was obtained from the medical records. We correlated ophthalmic findings in each patient with biochemical control as reflected by mean plasma homocyst(e)ine[7] and cyst(e)ine[8] levels since the beginning of therapy.

Results

Fourteen patients (seven males and seven females) were detected on newborn screening (group 1, Table 1). Their mean age at the start of treatment was 22·7 days, range 7 to 42 days. The mean period of follow-up was 8·2 years, range 3·9 to 15·3 years. Cases 10 and 11 were partially pyridoxine-responsive and the remaining 12 cases were pyridoxine-unresponsive. All patients required a low-methionine diet supplemented with cysteine.

Four patients were poorly controlled with respect to mean plasma homocyst(e)ine (cases 9, 12, 13, and 14) while case 9 was well controlled with respect to mean plasma cyst(e)ine. All patients had corrected visual acuities of better or equal to 20/30 None of the patients in group 1 have developed ectopia lentis. Cases 12 and 13, aged 15·3 and 8·1 years, who were poorly controlled with respect to homocyst(e)ine, have become increasingly myopic. Four patients have marked benign peripheral cystoid degeneration (cases 10, 11, 12, and 13). Case 14, aged 3·9 years, had an episode of bilateral optic disc oedema and ataxia during a period of poor dietary compliance; spontaneous resolution followed normalisation of biochemical control.

SELECTED CASES

Case 13 began treatment at 42 days and was poorly controlled because of poor compliance. At the most recent assessment this child was myopic (OD −6·5 sphere, +1·0 cylinder, axis 5°; OS −5·5 sphere, +1·0 cylinder, axis 170°), but one year previously refrac-

Table 1 *Summary of age data, major eye findings, and biochemical control for patients in group 1 (newborn screening)*

Case no	*Sex*	*Age therapy commenced (days)*	*Age now (years)*	*Mean biochemical control**		*Ocular abnormalities*
				Plasma homocyst(e)ine	*Plasma cyst(e)ine)*	
1†	F	35	14·2	Good	Good	—
2	M	22	4·4	Fair	Fair	Hypermetropia
3	M	21	6·3	Good	Good	—
4	M	13	5·5	Good	Good	Hypermetropia
5	F	15	6·3	Fair	Fair	Hypermetropia
6†	F	28	4·4	Good	Fair	Hypermetropia
7	F	8	8·8	Fair	Good	—
8	M	7	5·0	Good	Good	Hypermetropia
9†	F	26	7·5	Poor	Good	Hypermetropia
10‡	M	10	12·6	Good	Good	PCRD
11‡	M	36	13·5	Good	Good	PCRD
12†	M	42	15·3	Poor	Fair	Myopia, PCRD
13	F	42	8·1	Poor	Poor	Myopia, PCRD
14	F	13	3·9	Poor	Fair	Hypermetropia, optic disc oedema

*Mean biochemical control, for homocyst(e)ine (good <10 μmol/l, fair 10 to 15 μmol/l; poor <15 μmol/l), for cyst(e)ine (good >22 μmol/l; fair 12 to 21 μmol/l; poor <12 μmol/l).

PCRD=Peripheral cystoid retinal degeneration.

†Cystathionine-β-synthetase activity assessed—negligible or undetectable

‡Partially pyridoxine responsive

tion was OD +1·0; OS +1·0. The corrected visual acuity was 20/20 in each eye and there was no evidence of ectopia lentis. She had peripheral cystoid retinal degeneration extending circumferentially through 360° posterior to the globe equator.

Case 12 began treatment at 42 days and was poorly controlled since diagnosis. His corrected visual acuity was 20/30 in each eye and became increasingly myopic with time (1978: OD +0·75 sphere, +1·75 cylinder, axis 115°; OS +1·0 sphere, +2·0 cylinder, axis 60°; 1983: OD −2·0 sphere, +3·0 cylinder, axis 120°; OS −2·75 sphere, +2·25 cylinder, axis 30°; 1987: OD −8·0 sphere, +3·25 cylinder, axis 120°; OS −5·0 sphere, +3·25 cylinder, axis 50°). The lens examination was unremarkable and funduscopy showed peripheral cystoid retinal degeneration extending circumferentially through 360° posterior to the equator.

Five patients (three males and two females) were detected later in life (group 2, Table 2). Their mean age and commencement of treatment was 3·7 years with a range of 1·5 to 7 years. The mean period of follow-up was 9 years, range 4·8 to 15·8 years. Case 17 was pyridoxine-responsive, while the remainder were pyridoxine-unresponsive. Cases 15, 16, and 17 initially presented to the ophthalmologist with poor vision due to bilateral ectopia lentis. Case 19 presented at 1·5 years with an intracranial haemorrhage and seizures. Case 18 was diagnosed at 2·4 years after identification of homocystinuria in a sibling on neonatal screening. Ectopia lentis progressed or developed in all patients in group 2 despite good biochemical control. The corrected visual acuity was better than or equal to 20/30 in three eyes, 20/40 in four eyes, and 20/120 in one eye with strabismus. Visual acuity was indeterminable in case 19 owing to mental retardation.

Case 15 presented with bilateral symmetrical inferonasal ectopia lentis at 2·9 years. Despite tight biochemical control both lenses continued to dislocate downwards, and this was associated with increasing myopia (1985: OD −5·5 sphere, OS −3·50 sphere; 1987: OD −8·50 sphere, OS −5·5 sphere).

Case 16 presented at 4·8 years with bilateral symmetrical inferonasal ectopia lentis and high myopia. There has been progressive lens dislocation in both eyes despite tight biochemical control to the extent that the patient required aphakic correction of +14·50 dioptre spheres in each eye.

Case 17 was pyridoxine-responsive and presented with bilateral symmetrical superonasal ectopia lentis and compound myopic astigmatism at 7 years. Since then both lenses continued to dislocate, with an associated increase in myopic astigmatism despite tight biochemical control.

Case 18 showed normal appearances on eye examination when treatment began at 2·4 years of age. One year later a unilateral left inferonasal lens dislocation was present in the absence of trauma. So far the right lens has appeared normal. The corrected visual acuity was 20/20 in each eye, and there was bilateral peripheral cystoid retinal degeneration.

Case 19 presented with an intracranial haemorrhage, spherophakia, and simple myopia at 1·5 years. Within six months he was noted to have early bilateral superonasal ectopia lentis, which continued to progress slowly despite tight biochemical control. His latest refraction was OD −11·50 sphere, +3·50 cylinder, axis 90°; OS −11·0 sphere, +2·0 cylinder, axis 95°. In 1980 the refraction was OD −5·0 sphere, +3·0 cylinder, axis 85°; OS −5·50 sphere, +3·50 cylinder, axis 90°. Funduscopy showed marked peripheral cystoid retinal degeneration extending to the globe equator.

Discussion

Ectopia lentis is the ocular hallmark of homocystinuria due to cystathionine-β-synthetase deficiency[9] and may be preceded for several years by myopia.[10] The mechanism by which the observed biochemical abnormalities produce the clinical

Table 2 *Summary of age data, medical and major eye findings, and biochemical control for patients in group 2 (late detected)*

Case no.	*Sex*	*Age therapy commenced (years)*	*Age now (years)*	*Medical and ophthalmic findings at diagnosis*	*Mean biochemical control*		*Ocular findings now*
					Homocyst(e)ine	*Cyst(e)ine*	
15	F	2·9	8·7	Mental retardation myopia, ectopia lentis	Good	Good	Myopia, ectopia lentis
16	F	4·8	15·8	Myopia, ectopia lentis	Good	Good	Ectopia lentis, aphakic glasses
17‡	M	7·0	13·3	Myopia, ectopia lentis	Good	Good	Myopia, ectopia lentis
18	M	2·4	8·5	Mental retardation hypermetropia	Good	Good	L ectopia lentis, L anisometropia, PCRD
19†	M	1·5	17·3	Cerebrovascular accident myopia spheroplakia	Good	Good	Myopia, ectopia lentis, PCRD

†Cystathionine-β-synthetase activity assessed—negligible or undetectable.
‡Pyridoxine responsive.

features of this disorder has not been fully explained, but there is evidence to suggest that it is related to the abnormal levels of homocyst(e)ine[7] and cyst(e)ine.[8] Lens zonules normally have a high cysteine content, and its deficiency may affect normal zonular development, thereby predisposing to myopia and lens dislocation. Homocysteine inhibits cross-linkage in collagen and elastic tissue and predisposes to zonule degeneration. The lens dislocation is invariably bilateral and is frequently inferior, but the position is not diagnostic, as the lens may migrate in any direction.[11] In our five patients with lens dislocation the lens in three migrated inferonasally and in two superonasally.

The diagnosis of homocystinuria may be difficult, as the age of onset, severity, and pattern of clinical manifestations vary widely among affected patients.[12] Likewise homocystine levels vary widely, and tests based on methionine loading may confirm the diagnosis in suspected cases missed on routine screening.[13] The typical untreated homocystinuric is asymptomatic in infancy and subsequently develops ectopia lentis, mental retardation, skeletal disorders, and thromboembolic episodes which may be fatal. The prevalence and natural history of these complications remain uncertain owing to the short interval between original discovery and initiation of various therapies. Present limited evidence indicates that the advent of effective neonatal screening programmes, combined with the introduction of effective diet and pharmacological therapy in the neonatal period, has improved the prognosis However, the ophthalmic benefit of treatment initiated in the newborn period remains uncertain because of the small numbers of patients studied so far

None of our 14 patients detected on routine screening and started on dietary treatment within six weeks of birth have developed ectopia lentis over a mean follow-up of 8·2 years. Mudd *et al.*[5] suggest that the probability of ectopia lentis developing in untreated pyridoxine-unresponsive patients by 8 2 years is in excess of 70%. However, two poorly controlled patients within this group (cases 12 and 13) have recently developed myopia. This may be the harbinger of ectopia lentis in this subgroup, and longer follow-up is required.

The outcome in late detected cases whose treatment is initiated prior to the development of ectopia lentis is not clear, but two such cases (18 and 19) in our series developed ectopia lentis despite tight biochemical control within 1·5 and 0·5 years of initiation of therapy. Boers[14] followed up five such pyridoxine-responsive cases for periods ranging from 0·5 to 13 years and none developed ectopia lentis. Grobe[15] suggests that ectopia lentis occurs in such cases but to a milder degree Mudd *et al.*[5] state that therapy may reduce the lens dislocation rate in pyridoxine-responsive cases but may not confer statistically significant benefit on lens dislocation in pyridoxine-unresponsive patients. It is clear from our present data that ectopia lentis progresses despite tight biochemical control in late detected cases.

Ectopia lentis is bilateral in the vast majority of patients with homocystinuria. Case 18 in our series developed unilateral ectopia lentis within 18 months of beginning a diet and has been followed up for four years with no change in the position of the contralateral lens to date.

Benign peripheral cystoid retinal degeneration extending circumferentially to the globe equator occurred in six of our 19 patients No case progressed to degenerative retinoschisis. Ramsay and colleagues[16] suggest on the basis of histological studies that, in addition to ectopia lentis, peripheral cystoid retinal degeneration may also be observed as a characteristic clinical finding in some cases of homocystinuria. They also suggest that the pathogenesis of cystoid degeneration and that of ectopia lentis may be interrelated because of their common embryological origin. They note that the severity of the changes are age related and depend on patient survival. Peripheral cystoid retinal degeneration is the most common peripheral degeneration[17] present to some degree in all eyes after 8 years of age and gradually increases with age. In contrast to ectopia lentis and myopia we found no relationship between the age at start of treatment, adequacy of biochemical control, and peripheral cystoid retinal degeneration; but the number of patients are small and the follow-up period is relatively short. It is possible that patients with homocystinuria on an altered amino acid intake may be more susceptible to an acceleration of an otherwise common degenerative process.

Ocular complications are common in patients with homocystinuria. Ectopia lentis is the most significant in that it occurs in almost all cases, impairs visual acuity, and precipitates secondary sight threatening complications, including secondary glaucoma and retinal detachment. Lens extraction is probably associated with a greater incidence of ocular complications such as retinal detachment, and with intra- and postoperative mortality due to thromboembolic episodes. Newborn screening followed by tight biochemical control prevented ectopia lentis in 11 of 14 patients (mean follow-up 8·2 years). Myopia without ectopia lentis occurred in two of 14 patients with less tight biochemical control In contrast, ectopia lentis developed and progressed in five late-detected patients despite tight biochemical control. These results suggest that early treatment may significantly and beneficially alter the natural ophthalmic course of homocystinuric patients. The relationship between peripheral retinal changes and homocystinuria requires further evaluation.

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Problems encountered in recruiting patients to an ophthalmic drug trial

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SUMMARY Two clinical trials to assess the efficacy of two topical beta-blocker preparations involved the recruitment of 60 and 40 patients respectively. The greatest obstacle encountered in carrying out the trials was recruiting patients. This difficulty is reported in detail and comparisons are made with the experience of others who have met similar problems.

All who have carried out clinical research will be aware that the recruitment of patients often poses major difficulties. It is only too easy to overestimate the number of patients who will both agree to take part in any study and will satisfy the inclusion criteria. However, in spite of this difficulty being commonplace, there is little information in the ophthalmic literature on the likely scale of the problem We therefore took the opportunity of documenting the erosion of the number of patients originally identified as possibly being suitable for inclusion in two studies of the efficacy of two beta-blocker drugs. Our aim in quantifying the problems encountered is to give guidance to others undertaking similar studies.

The trials involved recruiting a statistically determined number of patients to allow comparison of the effects of the two preparations in the treatment of patients with either chronic open-angle glaucoma or ocular hypertension. The first study was a single-masked randomised crossover trial. The 60 patients were required to attend hospital on five occasions at three weekly intervals over a 12-week period. On three of these visits patients were required to arrive at the hospital at 9 am and stay until 5 pm. On the two remaining visits patients needed to spend no longer than half an hour in the hospital.

The second study was a randomised evaluation of both preparations in which the patients received only one of the drugs over a period of 12 months. The 40 patients were required to attend hospital for between 30 minutes and 2 hours on six occasions.

Materials and methods

The names of patients for possible inclusion in the studies were derived from three sources; the outpatients' diagnostic index, members of the medical staff, and the medical secretaries. Patients were

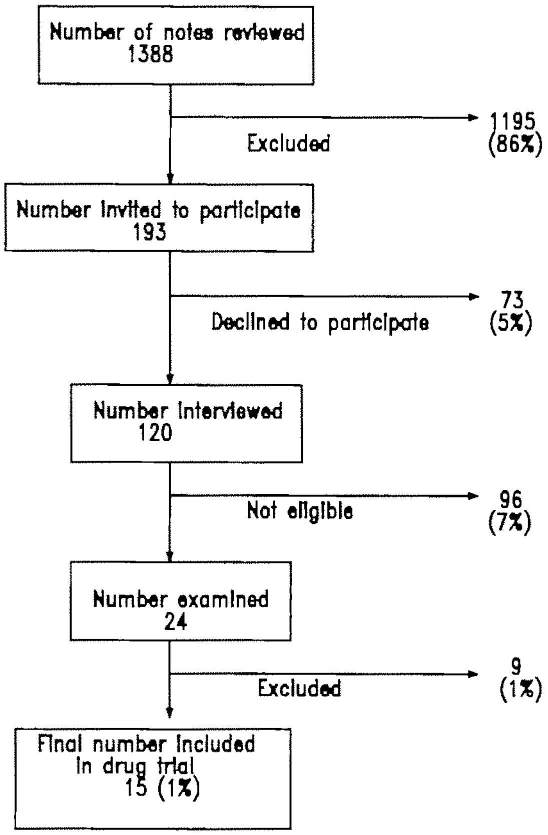

Fig. 1 *Summary of steps in identification of patients.*

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Table 1 *Definitions of chronic open-angle glaucoma and ocular hypertension*

Definition of chronic open-angle glaucoma:
(i) Intraocular pressure >21 mmHg
(ii) Glaucomatous cupping of the optic disc
(iii) A glaucomatous visual field defect
(iv) An open angle on gonioscopy

Definition of ocular hypertension:
(i) Intraocular pressure >21 mmHg
(ii) Normal optic disc
(iii) Normal visual field
(iv) An open angle on gonioscopy

considered if they were diagnosed as having either chronic open-angle glaucoma or ocular hypertension or if they were suspected of having glaucoma for any reason other than a raised intraocular pressure.

The recruitment of patients was carried out in the following four stages:

Stage A. The patients' hospital records were retrieved and the relevant notes were scrutinised. The records of patients not fulfilling the inclusion criteria were rejected.

Table 2 *Exclusion criteria*

(i)	Patients younger than 18 and older than 80 years of age
(ii)	Ocular diseases such as infection, inflammation, or corneal ulceration occurring within one month prior to the study
(iii)	Entry of foreign matter into the cornea within one month prior to the study
(iv)	Patients who wear contact lenses or who stopped wearing them within one month prior to the study
(v)	Intraocular operation or ocular injury within six months prior to the study
(vi)	All aphakic patients
(vii)	Patients with either secondary glaucoma or angle closure glaucoma
(viii)	History or evidence of a serious retinal condition
(ix)	History or evidence of bronchial asthma, chronic bronchitis, or other respiratory diseases
(x)	Cardiac insufficiency, myocardial infarction, cerebrovascular insufficiency, or aortic stenosis
(xi)	Sinoatrial or atrioventricular block as shown on an electrocardiogram
(xii)	Diabetes mellitus
(xiii)	Bradycardia (less than 55 beats per minute)
(xiv)	Melanoma or other malignancy that may give rise to ocular metastases
(xv)	Pregnant women or nursing mothers
(xvi)	History of intolerance to timolol
(xvii)	Patients who were judged by the attending investigator to be unsuitable for the studies
(xviii)	Prohibited drugs for concurrent medication were: other antiglaucoma agents apart from timolol; parasympathetic nerve stimulants; sympathetic nerve stimulants; carbonic anhydrase inhibitors; beta-adrenergic blocking agents; hypotensive agents (not including diuretics); tricyclic antidepressants; beta-adrenergic stimulants; oral and topical corticosteroids; monoamine oxidase inhibitors

Table 3 *Reasons for rejecting the case records of 1195 patients (stage A)*

	Number of case records	
	Number excluded	*Number remaining*
Original number of case records		1388
Glaucoma suspects	449	939
Multiple treatment	252	687
Notes missing	176	511
Serious eye disease	53	458
Narrow angles	45	413
Trabeculectomy	35	378
Lived too far away	27	351
On prohibited drugs	26	325
Respiratory problems	23	302
Diabetes mellitus	19	283
Secondary glaucoma	19	264
Cerebrovascular disease	16	248
Aphakia	15	233
Cardiac disease	12	221
Died recently	10	211
Low-tension glaucoma	8	203
Malignancies	7	196
Thyroid disease	3	193

Number of case records rejected=1195 (1388−193). 193 patients were then invited for interview. 120 patients agreed to be interviewed. 96 patients were found unsuitable (see Table 4).

Stage B. A letter was then sent to those patients who were thought suitable for inclusion in the studies. This set out the aims of the projects, and the patients were asked to return a slip indicating whether or not they wished to be contacted by telephone to be given further particulars.

Stage C. The returned slips were collected and the contents of the replies noted. The patients who indicated an interest in participating in the studies were invited to the hospital and interviewed.

Stage D. The patients were subsequently examined. After a full medical and surgical history had been taken, perimetry and electrocardiography were performed and the pulse and blood pressure were recorded.

This routine is summarised in the flow chart (Fig. 1). The definitions of chronic open-angle glaucoma and ocular hypertension as applied in these studies are given in Table 1. The exclusion criteria are set out in Table 2.

Results

The reasons for rejecting the case records of 1195 patients from an original 1388 (stage A) are shown in Table 3. Of the remaining 193 patients who were invited to take part in the studies (stage B) 120 agreed to be interviewed. At interview (stage C) 96 patients were excluded from the trials for the reasons shown in Table 4. Table 5 shows the reasons for a further

Table 4 *Reasons for 96 patients being excluded after being interviewed (stage C)*

	Number of patients	
	Number excluded	*Number remaining*
Number of patients		96
Prohibited drugs	25	71
Extensive field loss	14	57
Cerebrovascular disease	12	45
Respiratory disease	11	34
Diabetes mellitus	7	27
Unable to take time off work	5	22
Cardiac disease	5	17
Not actually instilling timolol	4	13
Unwilling to take part in study	3	10
On multiple treatment	3	7
Trabeculectomy	3	4
Bradycardia	2	2
Unreliable perimetry	2	0

nine patients being excluded after they were examined (stage D). Hence, only 15 patients were recruited from an original 1388 case records—a ratio of 1·92–5.

Discussion

The problems we encountered will be recognised by any one involved in clinical research. As Hamilton put it, 'In any investigation involving human subjects the most difficult part is getting hold of them.'[1] It was a great boon having an outpatient diagnostic index to which to refer in the first instance.[2]

In his review of the practical problems encountered in carrying out collaborative clinical trials Ederer[3] refers to the so called Muench's third law,[4] which states that the number of patients promised for a clinical study must be divided by a factor of at least 10. Several studies from other disciplines have documented the progressive loss of patients who were initially identified as likely to be suitable for inclusion in the trials. In the National Diet Heart Study[5] only 899 entrants to the trial were found after almost 20 000 people had been screened—a ratio of 1:22.

Table 5 *Reasons for nine patients being excluded after being examined (Stage D)*

Cardiac abnormalities diagnosed on electrocardiogram	3
Bradycardia	1
Changed to multiple treatment	1
Using hydrocortisone ointment for psoriasis	1
Over 80 years of age	1
Pathology identified on chest *x*-ray	1
Patient thought unlikely to complete study	1
Total	9

Other workers have had results even more akin to our own. In one component of the Hypertensive Detection and Follow-up Study[6] 5314 entrants were discovered among 436 679 contacts—a ratio of 1:82. In the Coronary Primary Prevention Trial[7] 3810 individuals took part out of the 436 679 people originally considered (1:115) Similarly, in the Veterans Administration Mild Hypertensive Study[8] 1012 participants were recruited from the 120 000 who were first approached (1:119). Finally, the recruitment to the pilot study of the Systolic Hypertension in the Elderly programme[9] was no more than 551 individuals from approximately 75 000 people originally contacted—a ratio of 1:136.

In view of our experience, and that of many others,[10] we suggest that the prudent research worker should divide by 100 the number of individuals he initially thinks may be eligible for a trial rather than by 10 as previously suggested. In this way later embarrassment will be more often avoided and fewer promises will be broken.

We thank Mr M J Absolon, Mr I H Chisholm, Mr J I McGill, and Mr C B Walker for permission to study patients under their care We are also greatly indebted to the junior members of the medical staff, the medical secretaries, and the staff in the Medical Records Department for their tremendous help in assisting us with this project Finally we thank the patients who took part in the study

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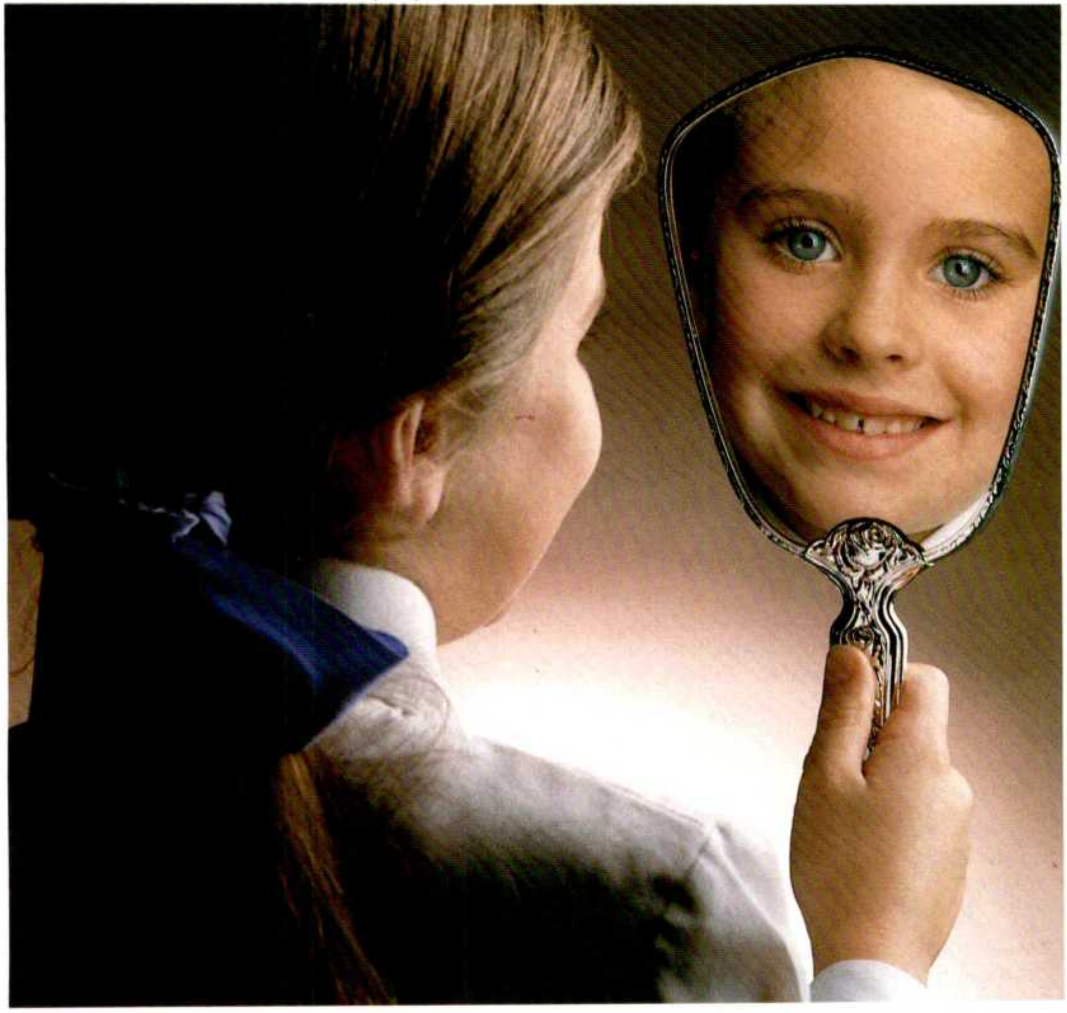

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Useful adjuncts for vitreoretinal surgery

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SUMMARY Many vitreoretinal procedures are performed in offices and hospitals where cost control is important. We describe three useful devices and techniques that facilitate these procedures at minimal expense and often greater convenience. These include an accurate method for localising the pars plana without the use of callipers, an inexpensive, reliable, pressure regulated air pump for fluid-air exchange, and an easy method for intraocular injection of silicone oil through 20 gauge instrumentation without the need for expensive pumps. These procedures and techniques should prove to be useful in the treatment of vitreoretinal disease.

Vitreoretinal surgical techniques are characterised by rapid technological change to treat eye disease optimally. Complicated retinal detachments associated with proliferative diabetic retinopathy and proliferative vitreoretinopathy are treated by vitrectomy, membrane dissection, long-acting gases, and in selected cases silicone oil. Endophthalmitis is often initially treated by vitreous aspiration and injection of intravitreal antibiotics. Pars plana injection of gas and air may be done in the office as part of pneumatic retinopexy and post-vitrectomy fluid-air exchange. We describe three instruments and techniques that should prove useful to the vitreoretinal surgeon. The techniques facilitate certain procedures which may now be done in the office or at hospitals that may not be fully equipped for vitreoretinal surgery.

Simple method for measuring the pars plana location in outpatient procedures

The pars plana ciliaris is considered to be the ideal site for the insertion of instruments and needles in posterior segment surgery and for intravitreal injections.[1] The pars plana occupies a zone between the posterior margin of the pars plicata ciliaris, approximately 2 mm posterior to the limbus, and the anterior border of the ora serrata. This zone is approximately 3 mm wide in the nasal quadrants and 4·5 mm wide in the temporal quadrants because of the varying location of the ora serrata.[2]

The pars plana entry site is usually made 4 mm posterior to the limbus in phakic eyes so as to avoid the crystalline lens.[1] In aphakic or pseduophakic eyes an entry is made 3·5 mm posterior to the limbus to provide an additional margin of safety to avoid making peripheral retinal breaks.

In outpatient procedures such as pneumatic retinopexy,[3] air-fluid exchange,[4] and intravitreal antibiotic injections[5] it is important to localise the entry site accurately These procedures must often be done in the office, sometimes on an emergency basis, where sterile callipers are frequently not available. We describe a method of marking the pars plana accurately with an easily identifiable ring imprint by means of a readily available, sterile, disposable syringe.

A lid speculum is placed between the lids. Retrobulbar or subconjunctival anaesthesia may be used. The conjunctiva is prepared with povidone-iodine and then irrigated with sterile saline. The distal end of a semi-rigid (plastic) 3 ml disposable syringe is pressed firmly and squarely on to the conjunctiva so that one edge of the tip is touching the limbus (Fig 1). This makes a ring indentation 4·0 mm in diameter. An intravitreal injection placed at the posterior edge of the mark will be accurately located 4·0 mm from the limbus (Fig. 2).

The syringe may also be used after opening the conjunctiva to mark the sclera. Should a more lasting mark be desired, a sterile, surgical felt-tip marking pen may be used to stain the tip of the syringe. Pressing the stained syringe tip on the sclera leaves a 4·0 mm ring mark.

This procedure provides a quick and easy method

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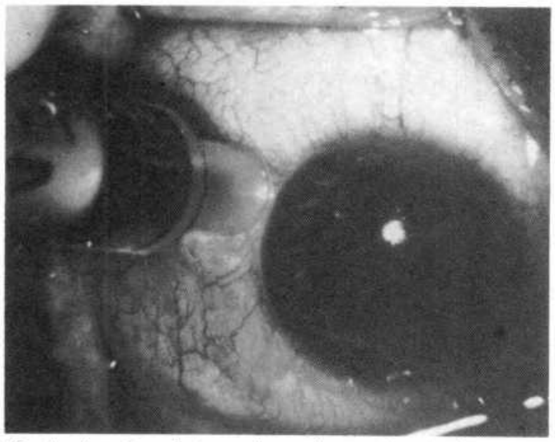

Fig. 1 *A syringe tip is used to make a conjunctival imprint with the anterior margin at the limbus.*

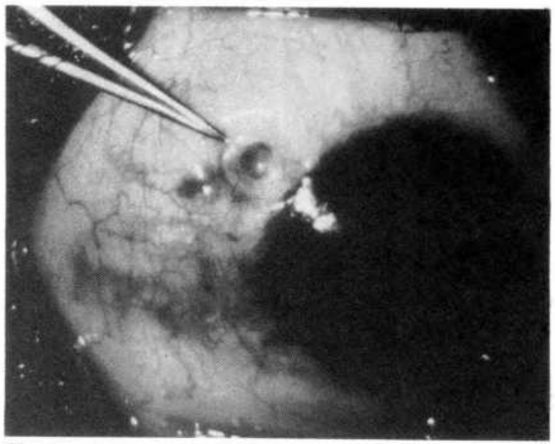

Fig. 2 *The forceps indicate the posterior margin of the ring imprint, which measures 4 mm in diameter and allows accurate placement of intravitreal injections.*

for accurately localising the mid pars plana zone for intravitreal injections in the outpatient setting. Semirigid plastic syringe tips have standard outer diameters of 3·925–4·027 mm as required by the American National Standard Institute/Health Industry Manufacturers Association.[6] The dimensions are the same for both Luer lock and Luer slip tips. These syringes are available in most hospitals and offices, are sterile, disposable, and inexpensive. Accurate localisation of the pars plana injection site in the office should decrease the incidence of complications associated with this procedure.

Simple, inexpensive, pressure regulated air pump for fluid-air exchange during pars plana vitrectomy

Automated fluid-air exchange is an important technique in the repair of complex retinal detachments.[7] Several air pumps are commercially available at a cost between $2000 and $2500 to infuse air into the eye at a constant controlled pressure during aspiration of intraocular fluid.[8–10] These units will keep the eye inflated at accurate pressures during intraocular manipulation, scleral plug exchange, sclerotomy closure, and pneumohydraulic reattachment of the retina. This is a major improvement over previous techniques of fluid-air exchange by means of syringes[11 12] or hydrostatic pressure from intravenous bottles to displace air from a second bottle.[13] We have designed an inexpensive apparatus for fluid-air exchange that infuses air at a precise pressure, is continuously adjustable, and is as effective as instruments of much greater cost.

An aquarium style air pump outflow line is connected to the eye via a sterile 0·2 μm filter (Millipore Corp, Bedford, MA), disposable tubing (Model K-50L, American Pharmaseal, Valencia, CA), and a vitreous infusion cannula. In this line are two ports. The first port acts as a bleeder line and is attached to a needle pressure relief valve. The second port is conected to a mercury or aneroid manometer borrowed from a sphygmomanometer (Fig. 3). The air pump has a rheostat to adjust gross changes in air flow. The rheostat is set during the initial case to deliver sufficient flow to prevent ocular collapse during rapid aspiration of vitreous chamber contents; thereafter the flow is the same with subsequent vitrectomies. The intraocular pressure is adjusted by turning the needle pressure relief valve. The manometer, calibrated in 2 mm increments, accurately measures the intraocular pressure in millimetres of mercury.

The components of this system can be purchased for less than $150, are portable, easily assembled, and reliable. As with expensive commercial models, this system maintains the intraocular pressure at a preset level during drainage of subretinal fluid, pneumohydraulic retinal reattachment, and other manipulations. This and similar units have been used as a primary instrument by the authors in over 100 vitrectomies in hospitals where cost control is important. It may also be used as a replacement should a primary commercial model become inoperable. We have found this unit to be safe and effective as a commercial fluid-air exchange pump with no complications and no noticeable difference in performance.

Useful technique for intraocular silicone oil injection

Silicone oil tamponade is a useful adjunct in the repair of complex retinal detachments after intra-

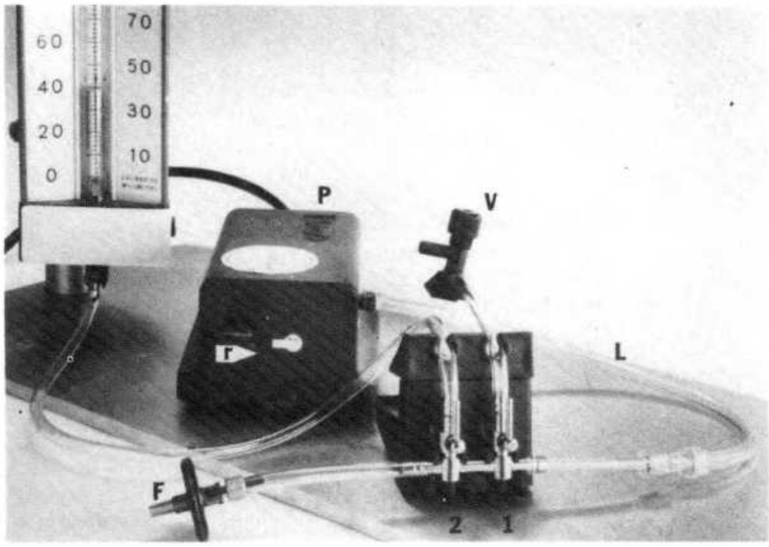

Fig. 3 *Front view of pressure regulated vitrectomy air pump. The air pump* (P) *outflow line* (L) *is connected to the eye via a sterile Millipore filter* (F) *which can be coupled to a standard K-50L infusion line. In the outflow line are two ports. The first port* (1) *is attached to a needle pressure relief valve* (V) *to adjust the intraocular pressure. The second port* (2) *connects to the manometer for accurate measurement of the intraocular pressure. The rheostat* (r), *on the air pump, adjusts gross changes in air flow.*

ocular membrane dissection.[14-16] Motorised pumps[17] have been developed to inject the highly viscous oil through a 20 gauge needle into the eye. These pumps are expensive, may be awkward, and many require a source of compressed gas. Shortened 16 and 18 gauge needles have been reported to make injection and aspiration of the oil possible without special pumps, but this technique necessitates a much larger pars plana opening.[18] We have found that warming silicone oil to body temperature, using a water bath blood warmer found in most operating rooms, allows manual injection, with little resistance, through a 20 gauge infusion cannula; no extra instrumentation or pumps are necessary.

MATERIALS AND METHODS

We measured the time of a falling sphere through a known length of 1000 centistoke polydimethylsiloxane in a graduate cylinder as described by Gibson and Jacobs.[19]

The Stokes equation

$$\text{velocity}_{\text{sph}}=2/9\cdot\text{gravity}\cdot(\text{radius}_{\text{sph}})^2\cdot\frac{\text{density}_{\text{sphere}}-\text{density}_{\text{oil}}}{\text{viscosity}_{\text{oil}}}$$

predicts that sphere velocity is an inverse function of liquid viscosity. The Walthers equation

$$\log\log(\text{viscosity}_{\text{liq}}+\text{constant}_{\text{liq}})=\text{constant}_{\text{liq}}\log\text{temp}_{\text{abs}}+\text{constant}_{\text{liq}}$$

shows that viscosity is inversely proportional to temperature.[20] With all other variables kept constant, measurements of sphere velocity as a function of liquid viscosity were performed with ceramic balls (density=3·88 g/cm^3) and nylon balls (density=1·32 g/cm^3) at constant temperatures of 25°C and 37°C. Care was taken to perform measurements in the middle section of the cylinder to allow the ball to achieve uniform velocity. Wall effect was kept to a minimum by selecting a ball of small size and dropping it in the centre of the fluid column.

In addition we measured the time required for 3 ml of silicone oil to flow under force through a 1 inch (2·54 cm) 20 gauge blunt needle attached via an arterial line to a syringe. A 1·14 kg weight was placed on the plunger of a vertically mounted syringe and measurements were taken at 23°C (operating room temperature) and 37°C. Other investigators have used a similar weight to approximate the force a surgeon could easily sustain.[18] This experiment was done to simulate closely the actual conditions encountered in using the oil delivery system in the operating room.

RESULTS

The mean times for the ceramic balls to fall 3·7 cm at 25° and 37°C were 4·67 seconds and 3·67 seconds respectively. Times for the nylon balls were 107·60 s and 83·15 s for the same respective temperatures. Sphere velocities at each temperature were computed and change in velocity recorded. because of the direct relationship of sphere velocity to liquid viscosity it was shown that increasing the temperature of the silicone oil resulted in an approximate 22% decrease in oil viscosity.

The mean time for 3 ml of oil to flow through a 20 gauge needle under 1·14 kg at 23°C was 22 minutes. At 37°C the time was reduced to 15 minutes, a decrease of 32%.

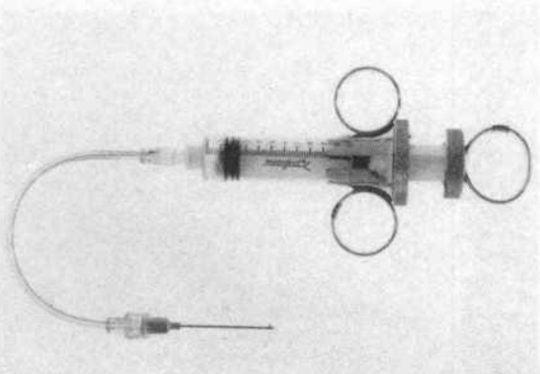

Fig. 4 *Manual delivery system for warmed medical grade silicone oil. The oil is placed in a 12 ml disposable syringe mounted in a convenient finger control attachment and is pushed through a 6 inch (15 cm) arterial monitor line with Luer lock connections (Medex Inc, Hilliard, Ohio, No. MX54OR) and 20 gauge blunt tip needle directly into the pressurised eye without the need of any pump.*

Discussion

The viscosities of several lubricating fluids, including silicone oils, at a variety of temperatures were examined by Murphy *et al.*[20] and plotted on a viscosity-temperature chart. From the straight line part of the chart they calculated the slope of a silicone oil having the same density as the oil used in our study (0·97 g/ml) to be 0·207. Using their chart to measure the change in viscosities from 25° to 37°C as a function of a given slope we calculated that an oil having a viscosity of approximately 1000 centistokes at 25°C will have a viscosity of approximately 750 centistokes at 37°C. This represents a percentage change in viscosity similar to our measured value.

The 1000 centistoke (measured at 25°C) silicone oil used in this study is the same oil viscosity used in the National Institutes of Health (NIH) approved National Silicone Oil Study and is in common use. We are aware that some surgeons use oil of higher viscosity. Increasing the temperature will decrease the viscosities of these oils as well, but the exact characteristics of other oils were not examined in this study. We[21] and others[22] have found that injection of oil is best done through a vitrectomy port with a short 20 gauge blunt needle while constant manual pressure is maintained (Fig. 4). However, this makes it necesary to inject under higher pressures than is achieved with larger bore needles. Temperatures in the operating room typically are set at 23°C, and the viscosity of fluids is higher than at standard room temperature (25°C). Our experiments show that under a constant force there is a 32% decrease in injection time when silicone oil is warmed from 23°C to 37°C.

Manual injection of silicone oil under these usual operating room temperatures is possible but requires considerable plunger force from the assistant. Warming the oil to 37°C with a readily available blood warmer decreases the viscosity, as shown in our study, and allows it to flow into the eye with less effort. This technique has the advantage that no additional instruments are required to express oil from the syringe. Although we did not test any higher viscosity oils, resistance to injection should theoretically be significantly decreased. There have been reports that emulsification can occur in lower viscosity silicone oil.[23] However, we have not experienced this with our method of injection. The 1000 centistoke silicone oil is prewarmed to body temperature only, and there should be no adverse effects attributable to this. It has been shown that light toxicity to the retina from the intraocular fibreoptic probe may occur during infusion of hyperthermic solutions[24] and we cannot recommend heating the oil to temperatures above 37°C. Because we inject the oil at the very end of the procedure there would probably be no phototoxicity. We have had no difficulty injecting silicone oil into the eye by this method and have used it, without complication, in the last 50 cases at our institution.

We thank Dr Douglas Magde, in the UCSD Department of Chemistry, for the use of his facilities and skilful direction on the viscosity experiments.

The authors do not have any commercial or proprietary interest in any of the devices, instruments or equipment discussed in this article.

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Losses of temporal modulation sensitivity in retinal degenerations

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SUMMARY Sensitivity losses in patients with retinitis pigmentosa (RP) have been attributed to a decrease in photopigment density, to a reduction in the number of photoreceptors, and also to a change in temporal response properties of the receptors. The sensitivity losses in patients with macular degeneration have also been attributed to a loss of photoreceptors. To test these explanations for sensitivity loss we obtained electrophysiological and psychophysical temporal modulation transfer functions (MTFs) on normal subjects in response to varying stimulus luminances and retinal loci. These stimulus manipulations did not duplicate the changes observed in the temporal MTFs of patients. The temporal response properties of the receptors were tested electrophysiologically by manipulating stimulus presentation interval. The results provided evidence for sensitivity losses in RP patients being due to alterations in the temporal response properties of the receptors.

Retinitis pigmentosa (RP) is a heterogenous group of retinal disorders which is associated with a progressive degeneration of the photoreceptors. Most patients with this disorder present with subjective symptoms indicative of a disorder of the rod system; however, there is ample evidence for cone system involvement as well.[1-4] Stargardt's disease is an autosomal recessive juvenile macular degeneration involving atrophy of the retinal pigment epithelium (RPE) and associated progressive degeneration of the photoreceptors. Whereas in RP peripheral vision is initially affected, in Stargardt's disease the macular area is primarily affected.[5,10]

In a previous study we assessed changes in cone system temporal sensitivity in patients with these retinal diseases using a focal electroretinographic technique (FERG).[6] Both RP and Stargardt's disease patients showed amplitude losses over the range of temporal frequencies tested; however, the pattern of loss differed between the two groups. RP patients with good visual acuities showed FERG amplitude losses at the higher temporal frequencies. In RP patients with decreased visual acuity their was an overall amplitude loss which was most severe at the higher temporal frequencies In contrast, patients with Stargardt's disease had FERG amplitude losses at both the low and high temporal frequencies, with responses to the mid-temporal frequencies being relatively spared (see insert to Fig. 3).

Various hypotheses have been proposed to account for the sensitivity losses of the cone system in these diseases. One explanation for RP attributes a major component of sensitivity loss to a decrease in quantum catching ability of the photoreceptors. This could result from a decrease in photopigment density, a misalignment of photoreceptors, or a shortening of photoreceptors. Histological examination of RP retinas, psychophysical studies of RP patients by colour matching techniques, and foveal densitometric studies all lend support to this explanation.[7,8,11-13]

Another explanation for the observed temporal sensitivity losses in RP patients suggests that time constants, or the dynamic adaptation properties, of the cones of the central retina are changed. This deficit would have the greatest effect on sensitivity to higher temporal frequency stimuli.[6,14,15]

The changes in sensitivity exhibited by patients with Stargardt's disease have also been explained by a decrease in quantum catching ability of the cone system. Indeed a recent foveal densitometric study of patients with Stargardt's disease reported low two-way densities.[16] Another explanation for the

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observed changes in Stargardt's disease suggests that, as central cones are lost, temporal sensitivity may be increasingly determined by peripheral retinal elements.

In this study we attempt to test experimentally these mechanisms of sensitivity loss by observing the changes in the focal electroretinogram (FERG) and psychophysically elicited flicker thresholds of normal subjects in response to changes in stimulus luminance and as a function of retinal location. We do not attempt directly to compare psychophysical and electrophysiological findings. Instead, FERG findings are compared with previous electrophysiological results obtained in RP and Stagardt's disease patients,[4] and our present psychophysical findings are compared with those of Tyler *et al* [14] from RP patients and with those of a Stagardt's disease patient reported on by Kayazawa *et al* [17] In a second experiment changes in response time constant were examined by measuring FERG response amplitude changes as a function of stimulus presentation interval. The results in normal subjects were compared with those in patients with RP.

Material and methods

Stimulus. An array of red LEDs subtending 9° at a viewing distance of 33 cm was centred in an illuminated Ganzfeld bowl. The LEDs were driven sinusoidally at a modulation depth of 100%. In each session five temporal frequencies ranging from 10 to 50 Hz were presented to the subject. The mean luminance of the stimulus array and surround could be adjusted independently (see Seiple *et al.*[4] for a complete description of the stimulus apparatus).

FERG recording. After pupil dilatation (1% tropicamide) and topical anaesthesia (0·5% proparacaine hydrochloride), monocular FERG responses were recorded with gold foil electrodes.[18] The ipsilateral ear served as the reference and the contralateral ear as ground. The other eye was occluded throughout the test.[19] The retinal potentials were amplified at a gain of 10 000 (Grass P511), and the filters were adjusted so that no signal attenuation occurred at the frequency of stimulation. Responses were signal averaged with artefact rejection (Nicolet 1170, n=128) and plotted on an X-Y plotter for analysis

Psychophysical testing. Threshold responses were obtained psychophysically with the same stimulus apparatus. The modulation depth of the LED array was slowly increased by means of a hand-held potentiometer until the subject reported detection of flicker. Four ascending trials were averaged for each subject at each stimulus condition

Normal subjects Two of the authors (WS and VG) and two students participated in this study. All were acquainted with the purpose of the experiments.

Stimulus manipulations. Experimental stimulus manipulations were chosen to test the hypotheses discussed above

(1) Decreased quantal catch hypothesis (decrease in the luminance of both the test and surround):

The effects of a decrease in the effective intensity of the stimulus on temporal modulation sensitivity were examined by placing a 0·3 neutral density filter in front of the tested eye This was done to mimic the effects of a loss of 50% of the visual pigment. This experimental manipulation equally reduced the test and the surround luminance. We predicted from previous psychophysical work that under the neutral density filter condition there should be decrease in sensitivity at all temporal frequencies, with sensitivity being less affected for the higher frequencies.[14 20 21]

(2) Relative contribution of the fovea (decrease in test luminance only):

In Stargardt's disease the central retina is primarily affected. Thus there might be relatively less contribution by the foveal elements and a greater relative contribution of more peripheral elements to the response Although this is hard to mimic in normal persons, we attempted to do so by reducing the mean luminance of the stimulus while leaving the periphery unchanged. The test luminance was decreased by 0·3 log unit, and measurements were obtained after adapting to the new level for 5 minutes.

The relative contribution of the foveal versus the peripheral elements was also tested by imaging the stimulus eccentrically. This was done in order to assess whether the temporal sensitivity of the peripheral retina in normal subjects resembled the pattern of temporal sensitivity observed in the diseased retina The stimulus was centred at 10° temporal to the fovea by directing fixation to an appropriate target on the Ganzfeld bowl.

(3) Changes in temporal response properties:

Changes in time constant of the diseased retina were examined by a paradigm in which the interval between two flashes was parametrically varied (a twin flash FERG paradigm). From our previous work[4] we expected that patients with RP would show an increased time constant. This should result in a prolongation of recovery to the first flash and a subsequent decrease in response amplitude to the second flash This effect should occur at longer interstimulus intervals in the RP patients than in the normals

In this experiment pairs of square wave pulses (10 ms duration) were presented by the focal ERG apparatus described above. The time interval between pulse pairs (interstimulus interval) was

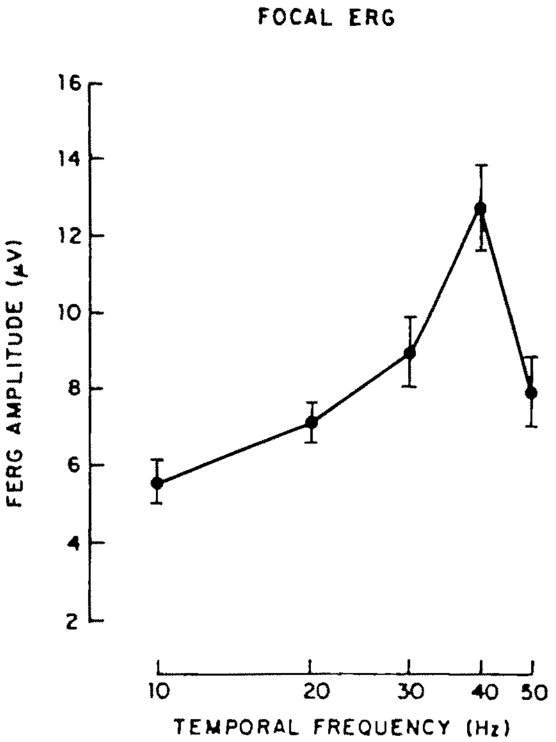


Fig. 1 *Mean amplitude (±1 SD) for normal subjects under the 'standard' stimulus condition (50 cd/m², 100% modulation, central fixation).*

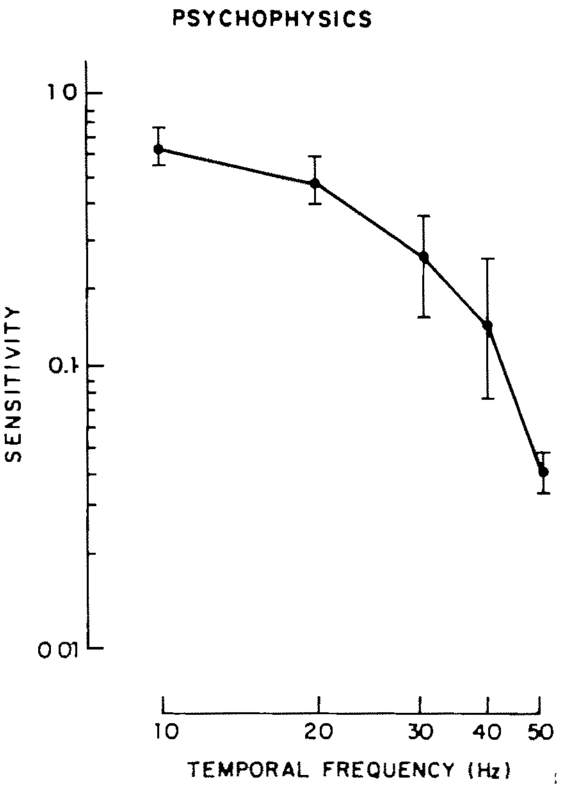


Fig. 2 *Mean sensitivity (±1 SD) measured psychophysically for the normal subjects under the 'standard' condition (50 cd/m², 100% modulation, central fixation).*

varied from 150 to 40 ms, with the intertrial interval constant at 500 ms. The ERG response to each stimulus condition was averaged (n=128). Six normal subjects and five RP patients (two females and three males ranging in age from 45 to 66) were tested in this experiment. The patients' visual acuities were 20/20 (n=2), 20/30 (n=2), and 20/70 (n=1) All patients had central fields subtending at least 10° measured with a III-4 white test light in a Goldmann perimeter. These patients were chosen to span a large range of macular involvement.

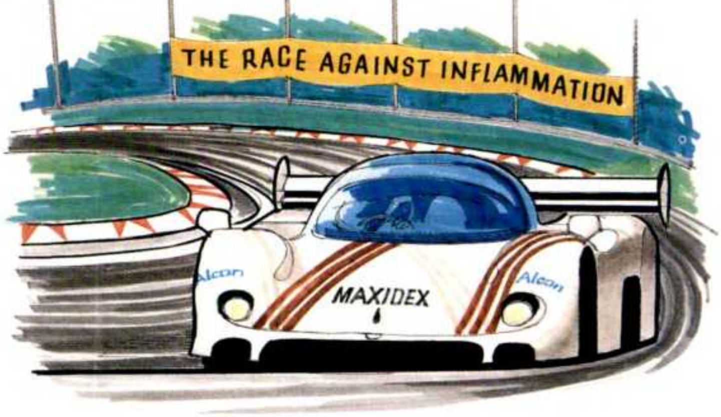
Results

The FERG responses to the various experimental manipulations were compared with FERG responses obtained under the 'standard' condition (mean luminance=50 c/m², modulation depth=100%, and the array centrally fixated). Percentage amplitude loss was calculated by the following formula ((standard response amplitude minus experimental response amplitude)/standard response amplitude× 100). For the psychophysically determined data percentage sensitivity loss was calculated in the same manner by comparing the flicker thresholds obtained under various experimental conditions with those obtained under the 'standard' condition.

Responses to the 'standard' condition. Mean FERG amplitude as a function of temporal frequency is presented in Fig. 1. For normal subjects there was a maximum response at 40 Hz, with a sharp high frequency and a shallower low frequency amplitude fall-off. These data are similar to the FERG data previously presented from this laboratory.[4]

Temporal frequency sensitivity obtained psychophysically is presented in Fig. 2. Peak sensitivity occurred at 10 Hz, with a loss of sensitivity at higher temporal frequencies. These data are similar to those previously presented.[14 20 21]

Decreased quantal catch hypothesis. Fig. 3 presents the mean percentage FERG amplitude losses for four normal subjects in response to a 0·3 neutral density filter placed in front of the tested eye. The presence of the filter resulted in a response amplitude increase at the low frequencies and an amplitude decrease at the intermediate temporal frequencies. However, at 50 Hz the percentage loss was less than that observed



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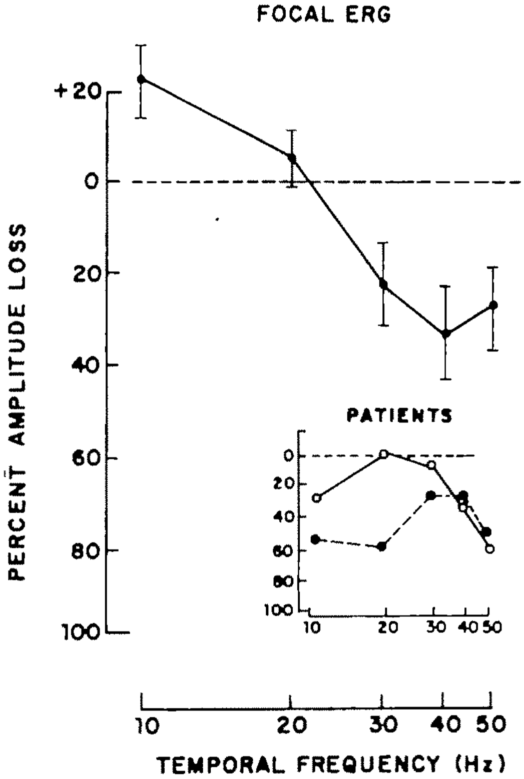

Fig 3 *Percentage FERG amplitude loss under the 0·3 neutral density filter condition. Amplitude to the experimental condition is compared with the amplitude obtained under the 'standard' condition. If the two conditions produced the same amplitude responses, the plot would be a horizontal line at 0% amplitude loss. A positive percentage amplitude loss indicates that the response under the experimental condition was greater than that obtained under the standard condition, and a negative percentage amplitude loss denotes that the response amplitude was less under the experimental condition. The insert shows the corresponding FERG data for RP patients (open circles) and Stargardt's disease patients (filled circles; from Seiple* et al.[4]*).*

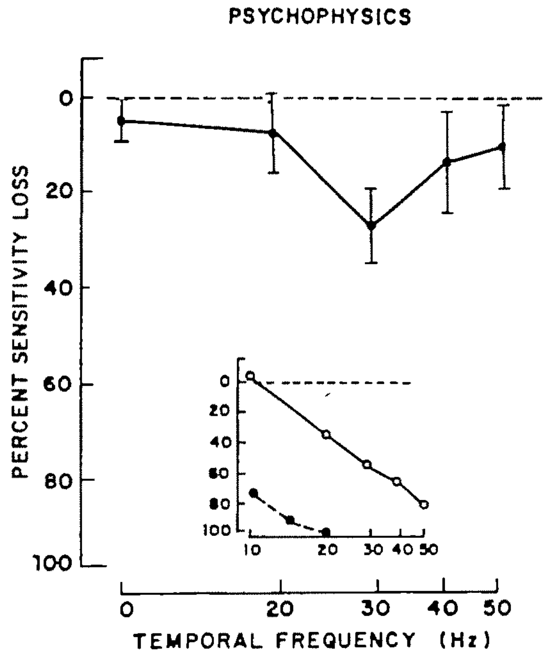

Fig. 4 *Percentage sensitivity loss measured psychophysically under the 0·3 neutral density filter condition. Sensitivity to the experimental condition is compared with the sensitivity measured under the 'standard' condition. If the two conditions produced the same threshold responses, the plot would be a horizontal line at 0% amplitude loss. The insert presents corresponding psychophysically obtained data for RP patients (open circles, from the data presented by Tyler* et al[14]*) and for one Stargardt's disease patient (filled circles; from Kayazawa* et al.[17]*).*

at 40 Hz. Psychophysical results for this stimulus condition are shown in Fig. 4. Sensitivity to 10 Hz was relatively unaffected, and there was a greater sensitivity loss at the middle temporal frequencies. Once again at 50 Hz the relative sensitivity loss was less that observed at the intermediate frequencies. The corresponding electrophysiological and psychophysical results for RP and Stargardt's disease patients are presented in the inserts in the figures for comparison. The inserts are from Seiple *et al.*[4] and represent FERG results obtained from 10 RP patients with good visual acuity (20/20) and from three patients with Stargardt's disease who had a visual acuity of 20/40 or better. We chose these patients for comparison because they showed the changes in temporal processing seen at the early stages of the diseases. The insert on Fig. 4, presenting psychophysical data, is the mean of 11 RP simplex patients of Tyler *et al.*[14] These authors did not distinguish individual patients on their graphical presentation, and therefore the average presented in our insert represents RP patients who had visual acuities ranging from 20/20 to 20/80. The high frequency specific pattern of loss, however, is representative of their findings. The insert data for Stargardt's disease have been derived from a single patient (VA=20/100) presented by Kayazawa *et al.*[17] To our knowledge this is the only Stargardt's disease patient in the literature who has been studied by psychophysical techniques.

Relative contribution of the fovea. Fig. 5 presents the FERG results of the reducing stimulus mean luminance (to 25 cd/m²). The largest response amplitude losses occurred for the mid temporal

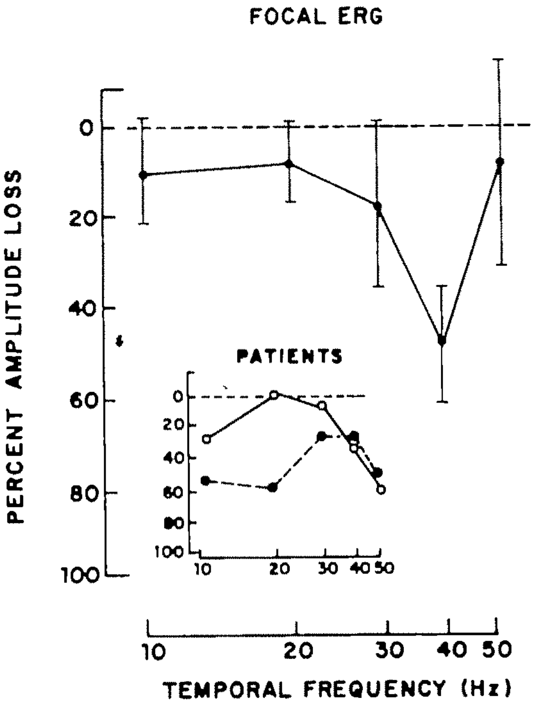

Fig 5 *Percentage FERG amplitude loss obtained when the stimulus luminance was reduced by half (25 cd/m²) FERG amplitudes obtained in response to this experimental condition are compared with those obtained under the 'standard' condition. The insert shows the corresponding FERG data for RP patients (open circles) and Stargardt's disease patients (filled circles; from Seiple* et al.[6]*).*

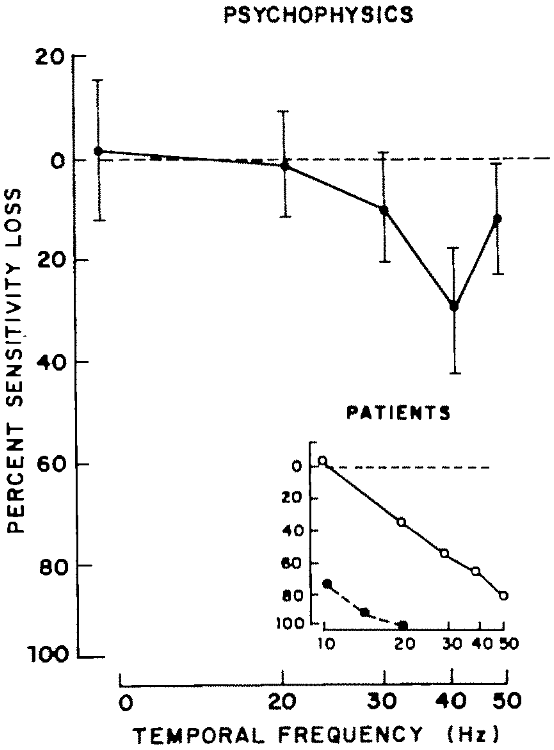

Fig. 6 *Percentage sensitivity loss measured psychophysically under the 25 cd/m² stimulus luminance condition. Sensitivity to the experimental condition is compared with the sensitivity measured under the 'standard' condition. The insert shows corresponding psychophysically obtained data for RP patients (open circles, from the data presented by Tyler* et al.[14]*) and for one Stargardt's disease patient (filled circles; from Kayazawa* et al.[17]*)*

frequency (40 Hz), with a relative sparing of both the low and high frequency amplitudes. Fig. 6 shows a similar trend for the psychophysical data. There is no change in sensitivity at the low temporal frequencies (10 and 20 Hz), and decrease in sensitivity was observed at 30 and 40 Hz. However, at 50 Hz the percentage loss of sensitivity was less than that observed for 40 Hz.

The results of stimulating more peripheral retina are presented in Figs. 7 and 8. Electrophysiologically there was an overall decrease in amplitude at all temporal frequencies (10 through 50 Hz). The decrease was minimal for the low temporal frequencies and highest for the mid temporal frequencies. As in the other stimulus conditions, the highest temporal frequency (50 Hz) responses showed relatively less percentage amplitude loss than the mid temporal frequencies (30 and 40 Hz). Psychophysically there was an increase in sensitivity at the higher temporal frequencies (>30 Hz) as compared with the 'standard' central fixations condition (Fig. 8).

Changes in temporal response properties (twin flash paradigm). In the normal subjects the amplitude of the response to the second flash gradually changed as a function of interstimulus interval. The complete curve is presented for only one normal subject (solid line in Fig. 9). Six normal subjects showed their lowest amplitude ERG responses to the second flash within the interstimulus interval ranging between 40 and 60 ms (filled circles, mean interval=49·75, SD 3·77). The complete data for one RP patient are shown by the dotted curve. Five RP patients (open circles, Fig. 9) with relatively good visual acuity showed their lowest amplitude ERG response to the second flash in the interval between 60 and 80 ms (mean interval=71·6, SD 6·06). The difference between the means of the two groups was statistically significant (Student's $t=4\cdot99$, $p<0\cdot002$, df=9).

Discussion

We have previously presented electrophysiological

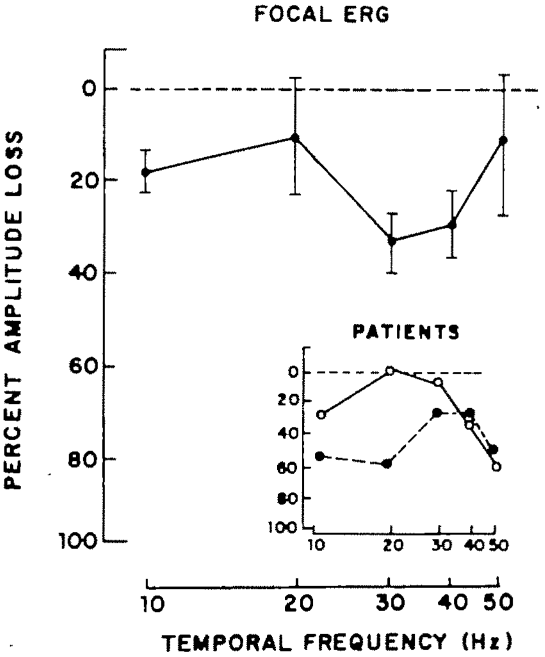

Fig. 7 *Percentage FERG amplitude loss under the 10° fixation condition. Amplitude to the experimental condition is compared with the amplitude obtained under the 'standard' condition The insert shows the corresponding data for RP patients (open circles) and Stargardt's disease patients (filled circles; from Seiple* et al [6]*).*

evidence that there is a progressive loss in FERG amplitude at the higher temporal frequencies in RP patients with good visual acuity.[6] From our current electrophysiological findings such a loss cannot be attributed to a decrease in the effective luminance of the stimulus—that is, decrease in quantum catching ability. The FERG responses obtained by experimentally manipulating the stimulus intensity showed relatively less amplitude loss at the highest temporal frequency compared with the mid temporal frequencies. Similarly, Massof *et al.*[15] in a later study, showed that the b wave latency changes at high temporal frequencies observed in a group of RP patients cannot be mimicked by decreasing retinal adaptation by changing the stimulus intensity.

The findings of a progressive FERG amplitude loss at high temporal frequencies in RP patients has led us to suggest that such losses may be due to a change in temporal properties of the receptors.[6] In fact our twin flash results (Fig. 9) provide evidence for an increased time constant These changes appear to have their origin in the outer retina, since FERG responses most probably reflect receptor activity.[22] Support for this contention is derived from a number of lines of evidence. Studies on the intact macaque monkey indicate that responses to high temporal frequency sinusoidal stimulation are derived from the outer retina.[23] Local ERG responses recorded in the monkey showed no intrusion of the ERG b wave, and both high and low frequency components of peripheral and central retinal stimulation have been shown to derive from the receptor activity.[24] In addition, Donovan and Baron[25] have shown that the corneal positive component of the monkey ERG recorded in response to a sinusoidally flickering stimulus is in fact a distal representation of the foveal local electroretinogram (LERG). Further support for the outer retinal origin of the fast flicker responses is the failure of glial cells to follow high flicker rates.[26]

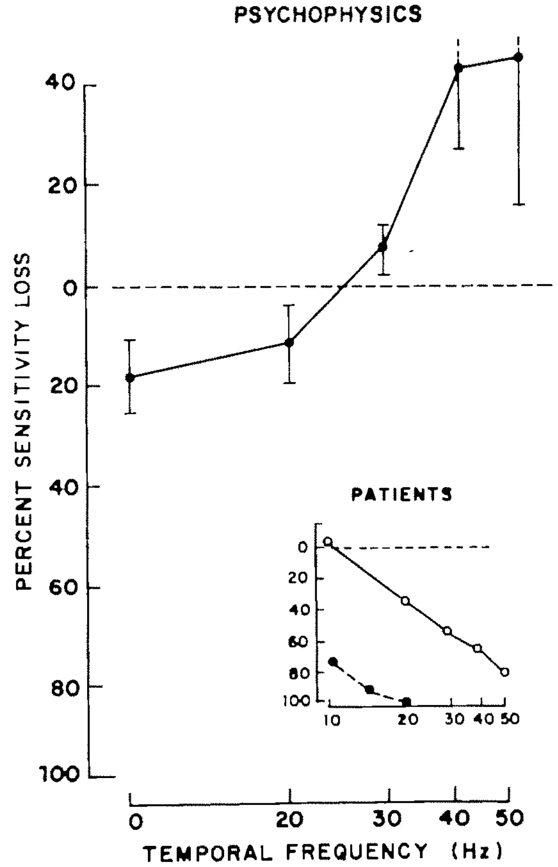

Fig. 8 *Percentage sensitivity loss measured psychophysically under the 10° fixation condition Sensitivity to the experimental condition is compared with the sensitivity measured under the 'standard' condition The insert shows corresponding psychophysically obtained data for RP patients (open circles, from the data presented by Tyler* et al [14]*) and for one Stargardt's disease patient (filled circles; from Kayazawa* et al [17]*).*

It is interesting to note, however, that the a wave

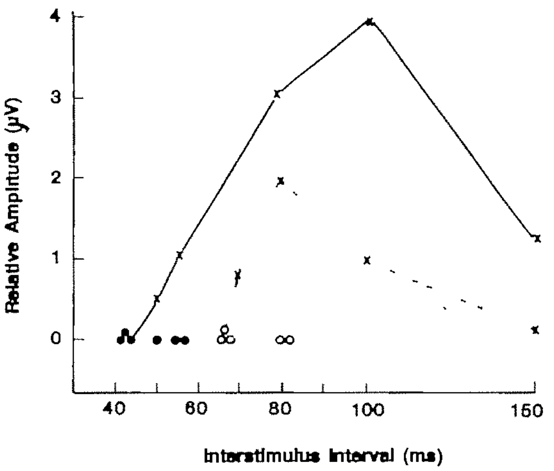

Fig 9 *Relative ERG amplitudes to the second of a pair of flashes for six normal subjects (filled circles) and five RP patients (open circles) plotted as a function of interstimulus interval The response amplitudes for all data have been normalised by setting each subject's lowest amplitude to 0 µV The entire curves for only one normal (solid line) and one RP patient (dotted line) are presented for comparison. For the other subjects only the corresponding interstimulus interval at which the response amplitude was lowest is indicated*

latencies (which reflect outer retinal processing) were normal in the RP patients studied by Massof *et al.*[15] This finding is not inconsistent with the proposed changes in time constant mentioned above. A delay in the time to recover following a flash may not necessarily affect time to respond (that is, latency). Instead it could primarily affect the amplitude of subsequent responses if these responses occurred within this prolonged refractory period. Indeed we have shown that the inhibitory effects of an initial flash are prolonged in RP patients (Fig. 9). FERG amplitudes have also been found to be reduced at high temporal frequencies (where stimuli follow at short intervals). However, the phase (latency) of the FERG for this group of RP patients was normal at all temporal frequencies regardless of visual acuity loss.[4]

Our electrophysiological findings in patients with Stargardt's disease are also not consistent with an explanation based on a decrease in quantum catching ability. These patients showed losses of response amplitude at both low and high temporal frequencies, with relative sparing of the mid temporal frequency response amplitude.[6] Again these changes in temporal responsiveness do not resemble the changes observed when the effective luminance of the stimulus was reduced. In addition, an explanation for these patients' temporal losses based on a relatively greater contribution of peripheral retina to the response must be rejected. The present data show that peripheral retinal stimulation results in the greatest decrease in FERG amplitude at mid temporal frequencies.

The pattern of psychophysical sensitivity loss in normal persons in response to decreased stimulus luminance also differs from the pattern of psychophysical loss found in patients. Instead of a progressive loss at high temporal frequencies in both RP and Stargardt's disease patients we found that the sensitivity loss at 50 Hz was relatively less than that at 30 or 40 Hz. These findings are in agreement with psychophysical data obtained by deLange[20] and Kelly.[21] Tyler *et al.*[14] have suggested that the differences in the patterns of psychophysical flicker sensitivity observed in their RP patients are due to changes in the responsiveness of the retinal elements. Using a probe flash technique, Greenstein and Hood[27] have also suggested that cone system sensitivity changes in their RP patients are due to a decreased responsiveness of retinal elements rather than a decrease in quantal catch.

Similarly, the pattern of psychophysical flicker sensitivity changes we observed by stimulating more peripheral retina does not resemble the pattern observed in Stargardt's disease.[17] Instead of a decrease in sensitivity at the high temporal frequencies, normal subjects show an enhancement of flicker sensitivity in the peripheral retina. This increased high frequency flicker sensitivity of the peripheral retina is consistent with previous psychophysical reports.[28,29]

CONCLUSION

Neither the psychophysical nor the electrophysiological data support an explanation of cone system temporal sensitivity losses observed in patients with RP or Stargardt's disease based *solely* on a decrease in the quantum catching ability of photoreceptors. We propose that the high frequency sensitivity loss of these patients may be based on changes in time constants. Our twin flash data suggest that this may indeed be the case.

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The visual evoked potential in acute primary angle closure glaucoma

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SUMMARY Visual evoked potentials (VEPs) were elicited from 29 patients who had experienced a previous attack of acute primary angle closure glaucoma. The VEPs were shown to be abnormal in at least one of the measures (latency, amplitude, contrast threshold, or slope) in 72·4% of affected eyes, whereas only 41·4% indicated obvious optic nerve damage. It is notable that 48·1% of fellow eyes with no (known) history of acute pressure rise also showed some form of VEP abnormality. The possible pathophysiological mechanisms operating in both affected and fellow eyes are discussed. It is concluded that, despite the presence of possible artefactual influences, the results probably reflect the presence of primary angle closure glaucoma.

The pattern electroretinogram (PERG), visual evoked potential (VEP), and contrast sensitivity as assessed by psychophysical (subjective) or electrophysiological (objective) methods have all been shown to be affected by primary open angle glaucoma (POAG) and to a lesser extent by ocular hypertension (OH).[1-37] While the effect of artificially induced acute intraocular (IOP) rises has been studied in humans,[38-40] to our knowledge there has been no research into the effect of acute primary angle closure glaucoma (PACG) on electrophysiological potentials or contrast sensitivity. A variety of field defects have been noted in acute PACG,[41] though clinical evidence of optic nerve damage in successfully treated cases is infrequent,[42,43] with cataracts possibly being the commonest cause of long-term visual loss.[41]

The aim of this study was objectively to assess visual function in a group of patients with acute PACG by means of the pattern reversal VEP to measure latency and the onset-offset VEP to assess contrast sensitivity. Particular attention was paid to those patients in whom there was no clinical evidence of optic nerve damage.

Material and methods

PATIENTS AND CONTROLS

Patients were included in this study if they had had an episode of acute PACG which had been successfully treated, usually by initial medical therapy followed by definitive surgery or laser treatment. Those with other coexisting eye or visual pathway pathology or visual acuities of less than 6/12 were excluded. All patients had a full ophthalmic assessment which included Goldmann perimetry and VEP investigation while wearing their optimum optical correction. Of the patients investigated 29 (5 male and 24 female) with an average age of 61 years (range 43–81 years) were found to fulfil the requirements. Two had had simultaneous bilateral angle closure; in these cases one eye at random was included in the study. Of the 29 affected eyes 17 had surgical iridectomies, nine had YAG laser iridotomies, and three had primary trabeculectomies. The 27 fellow eyes also had prophylactic treatment: 19 surgical iridectomies and eight YAG laser iridotomies. Retrobulbar or general anaesthesia were used for the surgical procedures. The reassessment was performed an average of two years after the acute attack (9 <1 year, 11 1–2 years, 6 2–5 years, and 3 >5 years). All patients gave their formal consent to participating in the study.

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VEP control data were taken from our database of 68 normal subjects (31 male and 37 female) in the older age range, the mean and standard deviation of the group being 61·0 and 8·6 years respectively.

ELECTROPHYSIOLOGY

The checkerboard stimulus was produced by a video pattern generator (Medelec) on a high quality TV monitor (Barco). In the first part of the test the pattern reversal mode of stimulation was used, checksize being 50′, contrast 95%, and field subtended, 17°×14°. Mean luminance was maintained constant at 10 Cd.m^{-2} and reversal rate was 2 per second.

The second part of the test, to measure contrast threshold, was performed with the onset-offset mode of stimulation. Pattern 'on' time was adjusted to be 40 ms and 'off' time 460 ms, that is, a repetition rate of 2 per second. Check size was 19′ where corrected visual acuity was ⩾6/9 and 25′ where visual acuity was <6/9⩾6/12. Recordings were made at four or five discrete contrast levels in the range 5% to 80%, the patients being given short periods of rest in between each measurement to minimise fatigue effects.

Silver/silver chloride disc electrodes were attached to the scalp in the following positions[44]: active—Oz, reference Cz, earth—Pz. Electrode impedances were measured prior to the test, these being <2 kohm in both active and reference leads. A Medelec electrophysiological recording unit was used to amplify, average, and store the evoked potentials. The amplifier bandwidth was set to 0·8–80 Hz, and either 64 or 128 epochs of 300 ms duration were averaged depending on signal amplitude. Two averages were obtained for each stimulus condition to check for consistency, and quantitative analysis was performed on the average of these two.

The latency of the 'P100' component[45] was measured in all investigations. With respect to amplitude a peak-peak amplitude measure was adopted. In the case of the pattern reversal VEPs it was that between P100–N150, in those to onset-offset it was between components CI and CII.[46,47] Monocular stimulation was adopted in all investigations, the subject maintaining fixation on a small LED marker attached to the centre of the screen (this being checked during the investigation by closed

Table 1 *Result correlation*

	Clinical				*VEP*					
	Ant. segment	*PAS*	*Field loss*	*Disc cupping*	*Lat*	*Lat diff.*	*Amp diff*	*Threshold*	*Threshold diff*	*Slope diff*
1	*	*								
2	*	*				*<	*>			
3	*	*		*	** f					
4	*	*					*			
5	*	*			** f	*		** f	*	
6	*						*	* f		*
7	*	*								*>
8	*	*	*	*				** f		
9	*					*<	*>			
10(Bı)	*	*	*		** f					
11		*		*						
12	*									
13	*	*				*	*	*	*	
14	*	*	*							*
15	*	*	*					** f		
16	*		*	*	*	*	*	*	*	*>
17	*	*	*		*	*		*	*	*>
18		*			* f	*<				
19	*									
20	*	*	*							*>
21(Bı)	*	*	*	*		*				
22						*		*	*	
23	*				** f					
24	*		*	*	** f		*	** f		*>
25	*				* f	*<	*>	*	*	*>
26										*>
27					** f	*<				
28	*	*	*	*	*					
29	*									

*Significantly affected **Fellow eye also affected >=Value greater than. <=Value less than. *f=Fellow eye significantly affected.
Lat.=latency. Amp.=amplitude. Diff =difference Bı=bilateral angle closure.

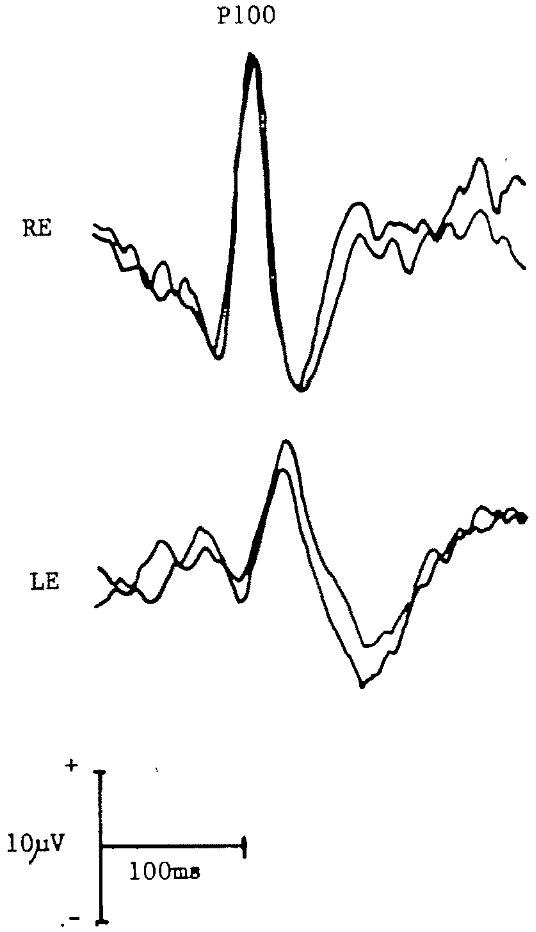

Fig. 1 *Pattern reversal VEPs from patient 16, who had previously experienced an acute attack of PACG in the left eye.*

circuit television). The non-stimulated eye was occluded with a patch. Before the test the subject was preadapted to the luminance of the blank screen for 5 minutes, which was the only source of illumination in an otherwise darkened room. The investigation was concluded with the measurement of the subject's pupil diameter under experimental conditions.

STATISTICS

In the establishment of control ranges for absolute VEP values data from one eye in each individual were selected at random.[28] This procedure was also adopted for the two patients who had undergone a bilateral attack of PACG. In the other 27 patients data from the 'affected' eye were chosen for analysis. With regard to interocular differences, the magnitude of this difference was used in the analyses.

Where the effect of pathology was assumed to produce excursions from normality in one direction only, for example latency increase, a single-tailed Student's *t* test analysis was adopted and the level of statistical significance set at the 1% level ($p \leq 0 \cdot 01$). If data distributions were observed to be markedly different in two groups being compared, an F test of variance ratio was performed, and, if significant, a correction[28] was applied to the number of degrees of freedom (df) being denoted in the analyses by *.

Results

CLINICAL

Twenty-six out of 29 affected eyes had either iris atrophy or peripheral anterior synechiae (PAS), while only two of 27 fellow eyes had PAS. Clinical evidence of optic nerve damage was present in 12/29 affected eyes, seven having optic disc changes and 10 having field defects, which were predominantly in the upper hemisphere (7/10). None of the 27 fellow eyes showed significant changes in the optic disc or visual field.

ELECTROPHYSIOLOGY

Pattern Reversal VEPs

VEPs elicited from the right and left eyes of female patient 16 (Table 1), who had an acute PACG episode in the left eye, are shown in Fig. 1. The form of the right eye's response was typical of that elicited to this stimulus mode, the clear positive 'P100' component being observed, which in general has monotonic form and nominal latency of 100 ms. In comparison, the response from the left eye was delayed and attenuated.

In Fig. 2 scattergrams of P100 latency for controls and the patients' affected and fellow eyes are shown in respective columns. As VEP latency is influenced by age,[23 30] the data were divided into two age-cells, 40–61 yr and 62–85 yr, to minimise this confounding factor and are illustrated respectively in Fig. 2(a) and (b). Thirty-seven and 31 of the controls fell into the younger and older age cells, respectively. For patients the corresponding numbers were 12 and 17. In comparison with control data the patient values showed a clear difference in distribution, which, interestingly, was the case not only for affected eyes but for fellow eyes too. Statistical analysis (the results of which are shown above each column of the scattergrams) essentially confirmed this visual impression, although the difference in means in the older age cell was not significant. (It is probable that this was due to broader data distribution and consequent statistical limitations rather than the absence of a real effect.) Upper confidence limits (cl) at the 99%

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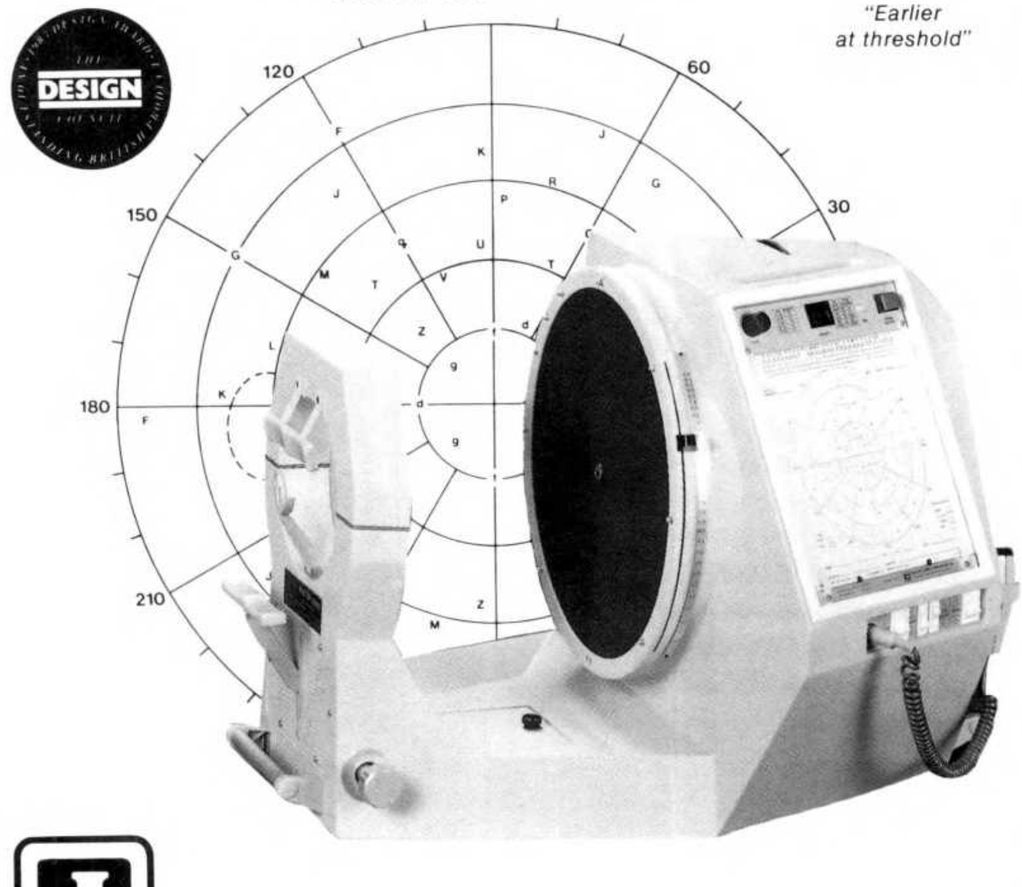

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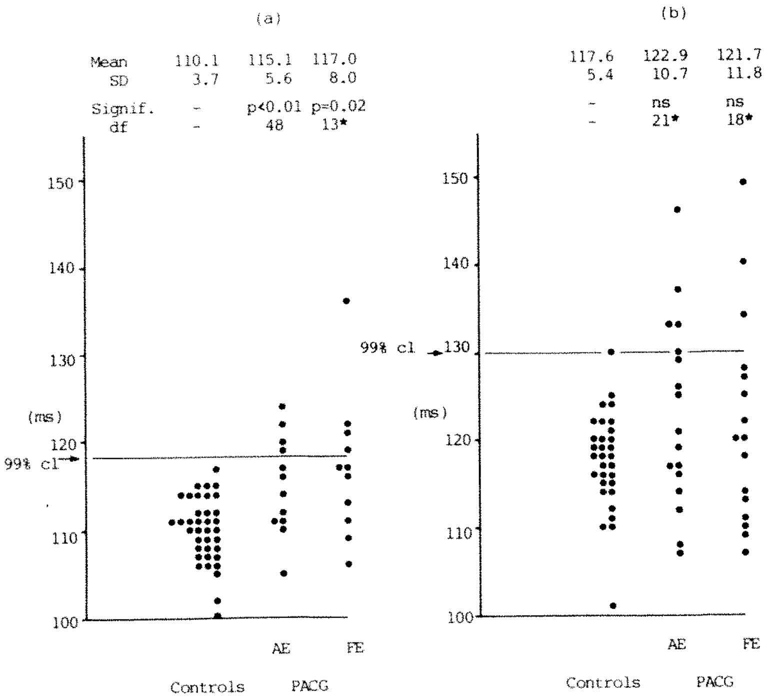

Fig. 2 *Scattergrams of P100 latency from controls and PACG patients in the 40–61 yr age-cell* (a), *and the 62–85 yr age-cell* (b). *See text for meaning of asterisk in Figs. 2, 3, 5, and 6.*

points were determined from control data and are shown drawn on each diagram, these being 118·7 ms for the younger group and 130·2 ms for the older. Thus it can be seen that in nine of 29 affected eyes (four and five of the younger and older groups, respectively) and seven of 27 fellow eyes (four and three, respectively) latencies were significantly delayed.

An important feature for investigation when monocular VEPs are elicited are interocular differences, which of course have much reduced intersubject variability in comparison to absolute measures. In Fig. 3(a) interocular latency differences are shown plotted for control and patient groups. This quantity is not age dependent, so all 68 controls and 27 unilateral PACG patients are presented on the same scattergram. A difference in distribution is, again, evident and confirmed by corresponding statistical analysis. With regard to individual cases, 10 of 27 (and one of the two bilateral cases, not displayed), were at or above the upper cl of 5·9 ms. Note, however, that five of the 10 had longer latencies in favour of the fellow eye.

As to VEP amplitude, no differences were observed in comparison with controls. However, interocular differences did appear to show some effect (see Fig. 3(b)), but the difference in group means was found to be not quite significant ($0{\cdot}02>p>0{\cdot}01$). Individually eight of 27 were significant (upper cl=4·4 μV), three of the eight having lower amplitudes in the fellow eye.

ONSET-OFFSET VEPS

Onset-offset VEPs from the left and right eyes of patient 16 are illustrated in Fig. 4(a). These responses, and in particular the CI–CII components, show a progressive reduction in amplitude as stimulus contrast is reduced. However, it can be seen that this attenuation is more pronounced in the left eye as compared with the right eye, an effect further illustrated when CI–CII amplitude is plotted against log contrast (Fig. 4(b)) and least squares regression lines are drawn through the data. A separation of the two regression lines is evident, and a difference in contrast threshold predicted. Extrapolation of the regression lines to the abscissa to determine threshold confirmed the increase in the left eye (6·0%) as compared with the right eye (1·8%) (a full discussion of contrast threshold determination by this method is given elsewhere[17]).

This procedure was performed on all control subjects and patients, and relevant threshold scattergrams are illustrated in Fig. 5(a). (Note that the usual convention of showing decreasing threshold, namely, increasing sensitivity, in the upwards direction on the diagram, is adhered to.) There appears to be a shift to higher thresholds in the patient data, notwithstanding the fact that log scaling inevitably produces a

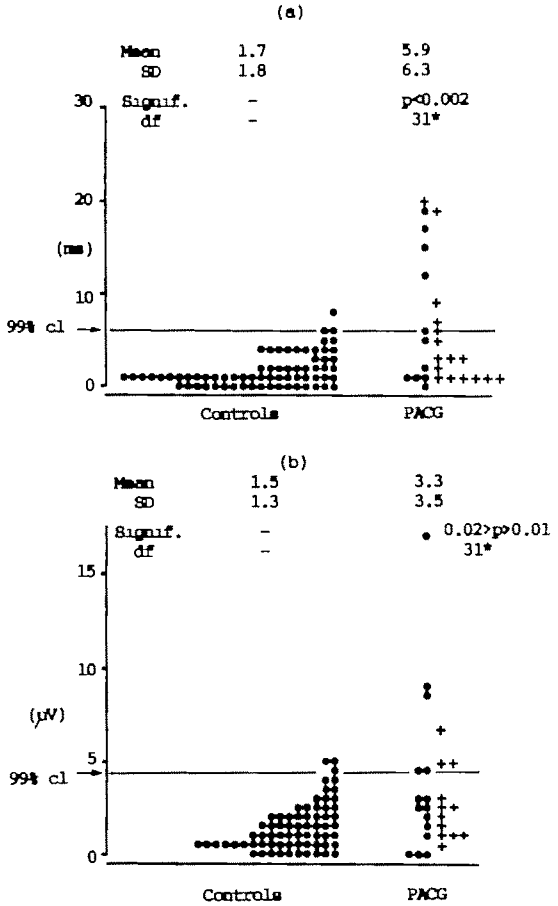

Fig. 3 *Scattergrams of interocular latency* (a) *and interocular amplitude* (b) *in controls and PACG patients. Note: symbol + denotes larger value in unaffected eye in diagram* (a) and lesser *value in unaffected eye in diagram* (b)

diagrammatic compression. Statistical analysis revealed that patient means were significantly different from control means not only for affected eyes but for fellow eyes as well. In relation to individual cases, nine of 29 affected eyes and five of 27 fellow eyes were above the upper cl of 4·8%.

Interocular threshold differences are displayed in Fig. 5(b). Although patient data appear to be biased towards higher values, statistically this was not quite significant. Individually, six of 27 cases showed an increase above the upper cl of 2·5%, all six showing the higher value in the affected eye.

The last evoked potential feature of interest is that of the slope of the regression line. This measure, however, showed large interindividual variability and did not reach significance in the patient group. Interocular measures, on the other hand, did show differences in distribution (Fig. 6), a feature confirmed by the statistically disparate group means. In terms of individual significances, nine of 27 equalled or exceeded the upper cl of 3·3 μV (log unit)$^{-1}$, and, of these, seven had the higher slope for the affected eye.

PUPIL SIZE

The pupillary diameter was observed to be significantly different in the affected eyes of patients as compared with controls (patient mean 6·1, SD 1·8 mm; control mean 3·9, SD 0·9 mm; p<0·001, df 95). With regard to fellow eyes, no difference was observed (patient mean 3·8, SD 0·8 mm).

SUMMARY OF RESULTS

A summary of the significant clinical and electrophysiological findings in each patient is shown in Table 1. In total, 24 of 29 patients (82·8%) had some form of VEP abnormality in either eye. With respect to affected eyes, 21 of 29 (72·4%) had abnormalities, and for fellow eyes the figure was 13 of 27 (48·1%). In the affected eyes of 17 patients who had either clinical signs or abnormalities confined to the anterior segment, 12 (70·6%) had some form of VEP abnormality. For the other 12 who had some form of optic nerve involvement (that is, field defects and/or disc cupping/pallor), 11 (91·7%) were detected in one way or another by the VEP.

Discussion

An accurate assessment of visual function in patients who have suffered an attack of acute PACG is fraught with difficulty. The group as a whole is elderly, and other coexisting eye or visual pathway disease is frequently present and can complicate any assessment of optic nerve function.[45] We specifically excluded patients with such pathology as well as those with poor vision to minimise any confounding influence on the VEP. In eyes with manifest optic nerve pathology (disc or field changes) a high correlation with VEP abnormalities (91·7%) was noted. In affected eyes with clinically no evidence of optic nerve damage (normal fields and discs) 70·6% showed some form of VEP abnormality, indicating the presence of covert optic nerve pathology.

These finding occurred despite the presence of two important artefacts which could have had the effect of concealing the full level of optic nerve damage. Firstly, the electrode montage used allows the cortical generator sites representing inferior field to dominate the full field VEP, whereas the majority of the field defects (7/10) in this study occurred in the superior field. In POAG this effect has been shown to

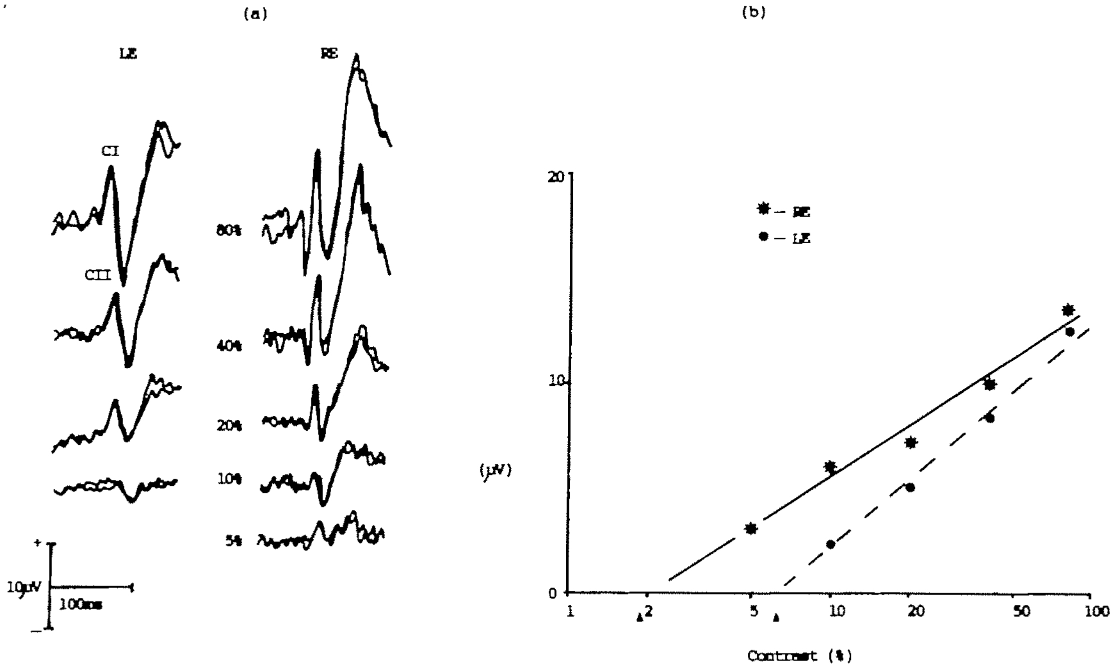

Fig. 4 *Onset-offset VEPs from patient 16 to different contrast levels* (a) *and the CI–CII amplitude-log*$_{10}$ *contrast plot of these data in* (b)

reduce dramatically the VEP detection rate in patients with predominantly upper field loss.[23] Secondly, the influence of increased pupil size due to sphincter paresis in affected eyes must also be considered. This increases retinal illumination, which has the effect of decreasing VEP latency[22] and enhancing contrast sensitivity, an effect which, again, serves to underestimate the level of optic nerve damage. In spite of these influences, overall 72·4% of affected eyes showed some form of electrophysiological abnormality, suggesting that significant optic nerve damage is extremely common after acute PACG and strongly implicating PACG as the cause of such optic nerve dysfunction.

The VEP changes in PACG are similar to those found in POAG, though one feature differs—the regression line slope of the amplitude-contrast plot. This is a suprathreshold measurement related to the difference in the luminance of the individual squares (spatial contrast) rather than the quality of the border between them, as it has been observed that optic blurring does not modify it but merely results in increased threshold.[37] At a retinal level this is likely to be related to the spike discharge rate of ganglion cells with centre-surround antagonistic properties.[23] In a study of patients with apparently unilateral POAG[23] 70·6% of 'affected' eyes were shown to have significantly lower slopes in comparison to their 'unaffected' eyes. It was argued that glaucoma had the effect of not only increasing threshold but also of suppressing suprathreshold firing, thereby decreasing the slope. However, in this study on PACG the changes were in the opposite sense—that is, 77·8% of our patients who had a significant interocular slope difference did so with the higher value in the affected eye. These findings can be explained if PACG has its main effect on threshold, affecting suprathreshold firing secondarily and to a lesser degree. The effect of raising threshold with unaltered suprathreshold firing would have the effect of increasing the slope. However, such conclusions have to be modified to some degree by the fact that they are based on interocular data and therefore assumed an 'unaffected' state for the fellow eye, an assumption not entirely justifiable, as we found 48·1% of these eyes showed an abnormality.

To comprehend fully the possible mechanisms of optic nerve damage in the two conditions it is necessary to be aware of the cellular layout in the anterior visual pathway. In primates retinal ganglion cells can be divided into two types—the magnocellular pathways and the parvocellular pathways.[33] The magnocellular pathways have large receptive fields, are most sensitive to low spatial-frequency gratings

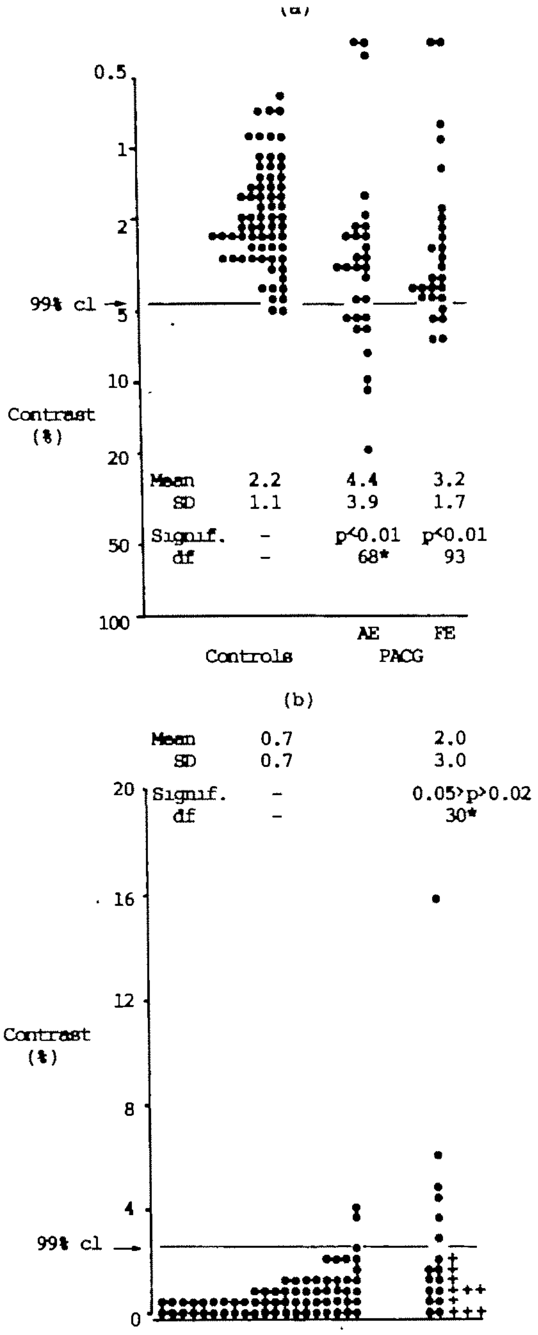

Fig 5 *Scattergrams of contrast threshold* (a) *and interocular threshold differences* (b), *in controls and PACG patients. Note: symbol + in diagram* (b) *denotes larger value in unaffected eye.*

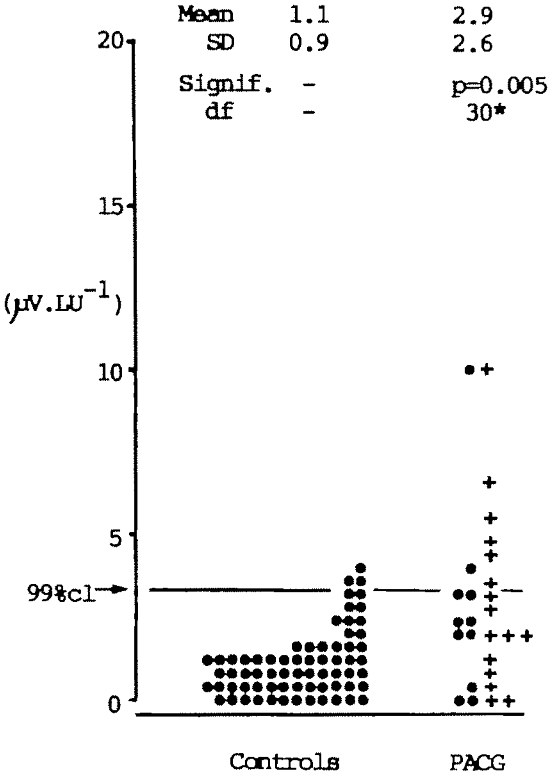

Fig. 6 *A scattergram of interocular slope difference in controls and PACG patients. Note: symbol + denotes lesser value in unaffected eye.*

(or large checks), function near to threshold, and synapse with large cells in the lateral geniculate body. These pathways consist of both X and Y cells, and are more highly contrast sensitive than the parvocellular pathways, which consist almost exclusively of X cells and synapse in the lateral geniculate body on small cells. The discovery in normal humans of a steady-state (on-off) VEP with low and high contrast limbs is in keeping with this theory of separate pathways (the low contrast sensitivity parvocellular and the high contrast sensitivity magnocellular) and suggests these pathways exist in humans.[34]

There is now both electrophysiological[35] and anatomical[36] evidence from experimentally induced glaucoma in primates that it is the Y magnocellular pathways which are the first affected by chronic increase of IOP. Our findings in PACG are in keeping with damage occurring to pathways which are highly contrast sensitive and function near threshold. This is synonymous with damage to the Y cell magnocellular pathway. Presumably with acute PACG the insult is relatively short-lived and changes are confined to this group of cells. However, with POAG the situation is different, in that we are dealing with a progressive condition Thus while the initial damage may occur in the Y cell magnocellular pathways, as the disease process progresses it will embrace the other pathways (X cell magnocellular and eventually parvocellular). So though the fundamental modes of optic nerve damage in POAG and PACG may be similar, the magnitude of the insult, in terms of the level of optic nerve dysfunction (as determined by the level of IOP increase and its duration) could still be different. Thus we might expect, as we have found here, the VEP to show similar changes in the two conditions, but with subtle differences indicative of differing levels of damage.

Finally with regard to the VEP abnormalities found in the apparently unaffected fellow eyes, we can only speculate on the cause of this. Mapstone and Clarke[57] proposed the theory that PACG occurs in a 'sick eye in a sick body', with the acute attack being only a single episode in the disease process.[58] Our findings of optic nerve dysfunction in fellow eyes in the absence of any definite history of IOP rise would appear to add support to their argument and suggest that the optic nerves are either abnormal as part of the disease process or perhaps more susceptible than normal eyes to minor variations in IOP. However, we must concede that as all measurements were performed after the fellow eyes had undergone prophylactic surgery or laser treatment, it is possible that in some cases the optic nerve damage was due to such factors as injury from the retrobulbar injection, ischaemic optic neuropathy due to general anaesthesia, or undetected acute IOP rise following YAG laser treatment.

The authors are grateful to Mrs Karen Seed, senior medical physics technician, who skilfully elicited a large proportion of the evoked potential data in this study

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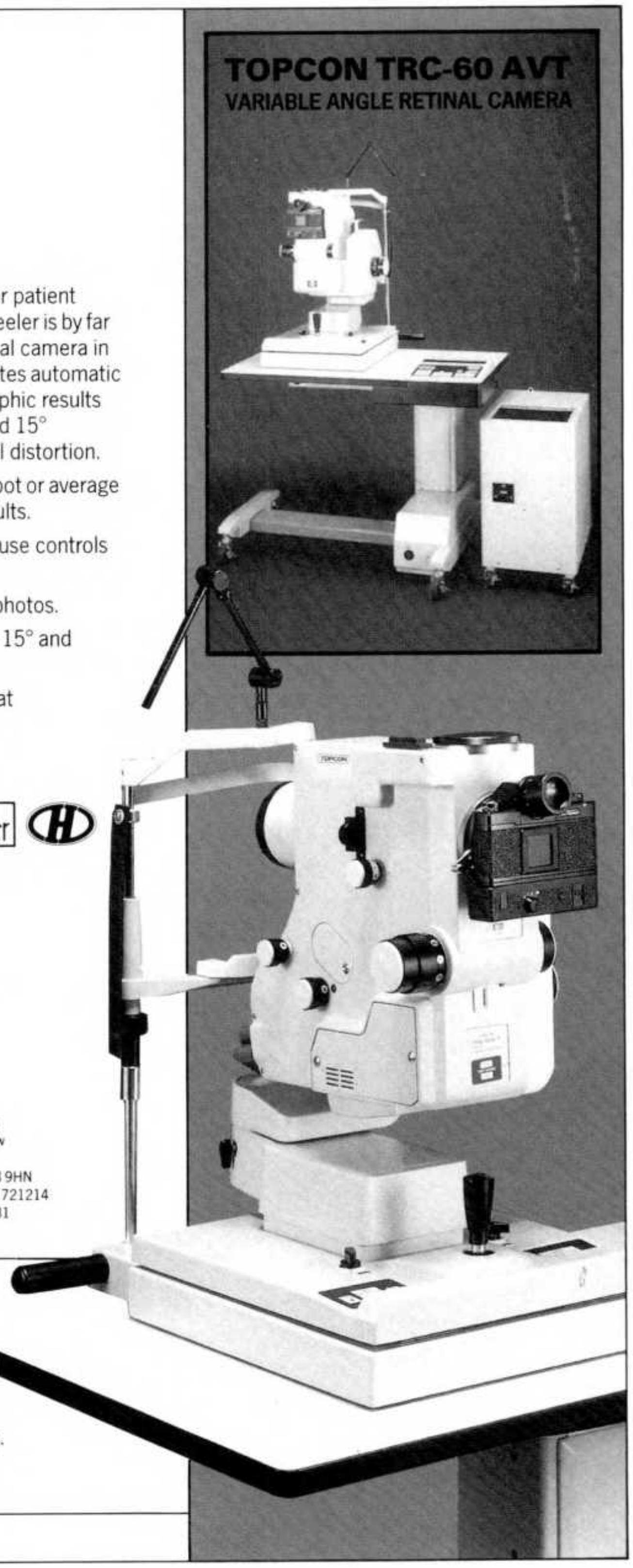

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Chart for visual acuity screening

D WONG AND S B KAYE

From the St Paul's Eye Hospital, Liverpool

SUMMARY The statistical basis underlying the use of several visual acuity charts is examined. A new chart which offers theoretical and practical advantages for visual acuity screening is described.

The measurement of visual acuity is an essential part of the ophthalmological examination and may be quite time consuming. For busy eye casualty departments, where the majority of patients often have visual acuities of 6/9 or better,[1] a visual acuity chart designed for speed and sensitivity is to be preferred. Visual acuity charts which have up to 10 characters to a line[2] are time consuming and perhaps not well suited for screening purposes.

The Snellen chart achieves a compromise by having fewer letters for the larger character sizes, but this makes the results obtained for each line no longer comparable. For example, if there are two letters on the 6/36 line and eight on the 6/6 line, then clearly, an incorrect response on the 6/36 line has a different significance from an incorrect response on the 6/6 line. The way the results are interpreted depends on the number of characters on each line.

A problem with the use of visual acuity charts lies in the convention used for recording visual acuity. The commonly used methods for recording visual acuity in the United Kingdom do not take into account incorrect responses on preceding lines. For instance, two patients may both have had their visual acuities recorded as 6/9 even if one patient gave an incorrect response on the 6/18 line and two incorrect responses on the 6/12 line while the other patient made no mistakes. In other words, the end point in such a test is ill defined.

An attempt to circumvent these problems has been to design a chart with five letters to a line read at four metres, allowing the examiner to assign an interpolated score for the logarithm of the minimal angle of resolution.[3] Although this improves the monitoring of visual acuity, the chart is large, cumbersome and still time consuming.

A further consideration is that individual letters have different degrees of difficulty.[4-6] Clues to their identity are given by the overall shape of the letter. For example, a base down triangle is often read as the letter A, a base up triangle as the letter V. In other words the psychic tasks of recognition may enhance visual acuity beyond the level of pure resolution.[4] Sloan *et al.*[5] assigned each letter a difficulty score based on how often that letter is read correctly at the visual acuity threshold (Table 1). Most of the commonly used charts in the United Kingdom take no account of these scores in their design.

Further problems arise when clinicians have different criteria as to what is considered a mistake. Some would pass an N for an H, a C for an O, an M for a W, etc, while others have more rigid criteria. Moreover, a major source of error is that patients often remember the letters of a given chart from previous examinations or when the same chart is used for testing both eyes. This problem can be overcome by having separate charts on a rotating box as is usually the case, or by having computer generated symbols.[1]

For screening visual acuity a chart that is easy to use, sensitive, and giving results that are not open to misinterpretation is required. We describe here a

Table 1 *Difficulty scores assigned to letters*

Sloan letter	*% Correct at threshold*
S	70·6
O	71 0
C	71·4
D	79·5
K	82 1
V	84·6
R	86·3
H	89·3
N	91·6
Z	94·0

The degree of difficulty of the Sloan letters as determined by the percentage correct at threshold is shown.

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visual screening chart using paired Sloan letters and discuss the statistical basis underlying the measurement of visual acuity.

Statistical analysis

Consider the null hypothesis that 'a subject is unable to see the letters on a Snellen chart and guesses the answer.' If one letter is presented the probability of guessing correctly is 1/26 (0·0385) and the probability of guessing incorrectly is 25/26 (0·9615). If 2 letters are presented, the probability of 2 correct responses is $(1/26)^2$=0·0015, 2 incorrect responses is $(25/26)^2$=0·9246, and the probability of one correct and one incorrect response is 2×(1/26)×(25/26)=0·0740. The probability of obtaining 2 correct responses from a line of 6 letters is $15\times(1/26)^2\times(25/26)^4$=0·0190, whereas the probability of giving 6 correct responses from the same line is markedly less at $(1/26)^6$=0·000000032.

This stringent demand for accuracy is at odds with other psychophysical tests or forced choice situations, or indeed with most of the clinical evidence on which our medical judgment is based. A more usually accepted scientific level of significance is $p<0{\cdot}05$ or $p<0{\cdot}01$, which is approached by using a chart with fewer letters per line.

An alternative null hypothesis states that 'although a subject is able to respond correctly an incorrect response is intentionally given.' To reject this null hypothesis it is necessary to demonstrate that a series of wrong responses is significant. The probability of an incorrect response when one letter is presented is 25/26=0·9615, and thus it would require a line of 118 letters, that is $(25/26)^{118}$, before significance is reached. In other words 118 incorrect responses are so unlikely that the patient is probably malingering. A Snellen chart with up to a maximum of 10 letters per line is thus inadequate for deciding if a patient is malingering.

If a similar statistical exercise is applied to the E test, a different picture emerges. In this chart the letter E is presented in one of four possible directions so that the probability of a correct response is 1/4=0·2500 and an incorrect response 3/4=0·7500. To achieve significance $p<0{\cdot}01$ in favour of a patient being able to see, a series of 4 correct responses needs to be given $(1/4)^4$ ($p=0{\cdot}0039$). Hence a minimum of 4 Es need to be presented. Similarly to prove that a patient can see a line when an incorrect response is given requires 17 consecutive incorrect responses to achieve significance—that is $(3/4)^{17}$=0·0075. The Landolt ring, which is also used in one of four directions, is subject to the same analysis.

In general the more symbols there are to choose from the easier it is to prove and the harder it is to disprove that a subject can see when correct responses are given.

Although only theoretical, these analyses suggest that the use of alphabets with 26 letters is economical. There are, however, a number of considerations which need to be taken into account when using a Snellen chart. Firstly, not all 26 letters are used. This should not in itself affect the validity of the statistics provided the subject is unaware that certain letters never appear on the chart, so that 26 options remain. Secondly, as previously mentioned, clinicians may count certain incorrect responses as correct, so that the number of possible options falls below 26. Nevertheless, even if it were assumed that the total number of options were as few as 10, then the probability of 2 successive correct responses when 2 letters are presented is still 1/10×1/10 or 0·01. The statistical considerations given above suggest that 2 letters per character size is sufficient to achieve significance ($p<0{\cdot}01$) when measuring visual acuity. If a subject reads both letters correctly, there is little point in presenting more letters on that line, because significance has already been reached. It would be more logical to move on to the next character size. If both letters are read incorrectly, again there is little point in testing more letters of the same size, for it would require another 205 wrong responses before one could conclude that the subject can see. It is more likely that the subject will volunteer that he or she cannot see the letters.

Using a chart with two letters for each character size, one would record the lowest Snellen fraction for which both letters are correctly identified. If with the succeeding character size both letters are incorrectly identified, the visual acuity would be recorded as that of the preceding Snellen fraction. This indicates that the probability of having arrived at this result by chance alone is well less than 1:100. If, however, only one of the letters of the succeeding character size is correctly identified, the visual acuity should still be recorded as that of the preceding Snellen fraction. This is because the last response obtained is not significant in that the probability of having identified this last letter by chance alone is approximately 1 in 10. For example, if both letters are correctly identified for the 6/9 character size, the visual acuity is recorded as 6/9. If, however, one letter is incorrectly identified on the 6/9 character size, the visual acuity should be recorded as 6/12.

Design of a new chart

We have used paired Sloan letters for each character size to construct a chart with the letters horizontally disposed in two lines with the following features:

1. *Two letters per character size.* As stated above,

Table 2 *Differences in difficulty scores of paired Sloan letters*

Snellen fraction	*Paired Sloan letters*	*Difference in their difficulty score (%)*
6/60	C S	71 4–70·6=0·8
6/36	V K	84 6–82·1=2 5
6/24	N Z	94 0–91 6=3·4
6/18	D K	82 1–79 5=2·6
6/12	O S	71 0–70·6=0 4
6/9	N H	91 6–89·3=2 3
6/6	V R	86·3–84 6=1 7

The difference in the difficulty scores between the Sloan letters of each pair used in Fig 1 is shown. This difference does not exceed 3·4% The likelihood is that either both or neither of the letters comprising a pair will be correctly identified Similar charts can be constructed based on the difficulty scores determined by Sloan.¹

two letters per character size is sufficient to achieve significance ($p<0{\cdot}01$) when measuring visual acuity.

2. *Paired Sloan letters*. Paired Sloan letters are chosen and their difficulty scores are used to construct the chart. Letters having similar difficulty scores are paired so that they are equally difficult (or easy) to recognise (Table 2). The advantage of this is that the subject will most probably identify the letters either both correctly or both incorrectly. This in turn, would minimise the occurrence of results such as 6/9−1 or 6/9+1 etc.

3 *Horizontal weighting*. The letters in the chart are horizontally disposed in two lines. By positioning bigger letters on the same line as some of the smaller, the crowding phenomenon associated with amblyopia may be detected. An additional advantage is that testing time may be further reduced by starting with the second line of smaller characters (that is, 6/18 onwards) since most patients have vision better than 6/18.¹

Use of the chart

The chart in Fig 1 has seven pairs of Sloan letters proportionately equivalent in size to the Snellen fractions 6/60 to 6/6. The letters of each pair have similar difficulty scores. The subject is asked to read along a line from left to right. Visual acuity is recorded as the equivalent Snellen fraction of the last pair of letters correctly identified.

Discussion

Visual acuity charts are used for many different purposes, such as refraction, screening, and monitoring changes in visual function. No chart serves all these purposes. For screening, sensitivity and speed are of importance, whereas the monitoring of subtle changes in the presence of disease demands a chart of high specificity. A sensitive test yields few false negatives—that is, patients who cannot see the letters and yet give correct responses. A test which is specific has few false positives—that is, patients who can see and yet give incorrect responses. In designing a visual acuity chart the more characters or lines used the greater would be its sensitivity and specificity at visual threshold. For example, if threshold is defined as 50%, the situation is analogous to tossing a coin; the results would approach threshold the greater the number of tests performed (or letters used). Conversely, the fewer the number of letters used (fewer tests performed) the more likely it is that chance will prevail, producing both more false positives and false negatives.

The sensitivity and specificity are therefore also dependent on the defined threshold or the endpoint of the test. If the endpoint is 'stringent', requiring a patient to get all the letters correct on every line, the

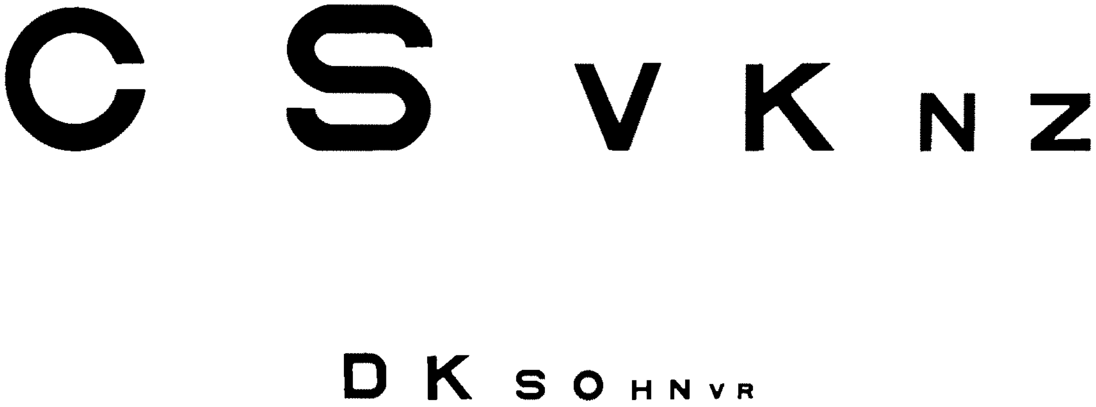

Fig. 1 *Chart with paired Sloan letters*

number of false positives would increase while the number of false negatives would decrease. In other words, the specificity falls while the sensitivity rises. This is used to our advantage with the proposed chart in that the decreased sensitivity resulting from using only 2 letters per line is compensated for by raising the threshold. In effect this chart uses a suprathreshold endpoint which reduces the ambiguity of the test and the interpretation of the results. The clear advantage of this test is that the testing time is markedly reduced.

CONCLUSION

The proposed chart represents a compromise between sensitivity, specificity, and time. It has been designed with the following features: (1) it has a suprathreshold endpoint; (2) the results obtained are not open to misinterpretation and have a defined statistical significance; (3) it is easy to use and time saving.

We would recommend that this chart be used for screening purposes.

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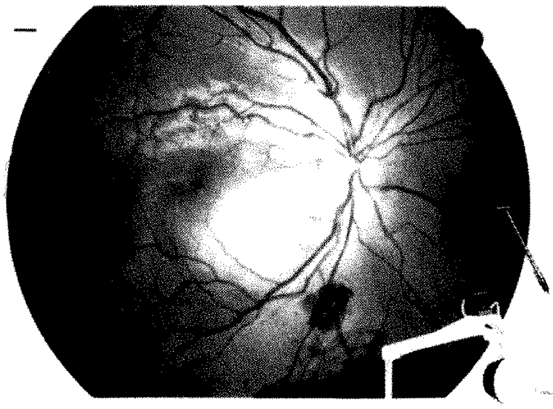

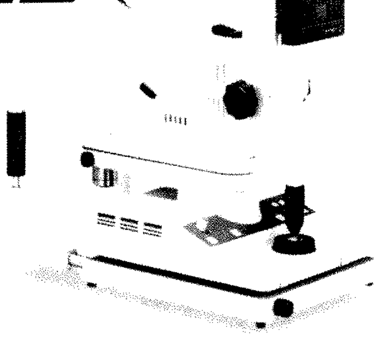

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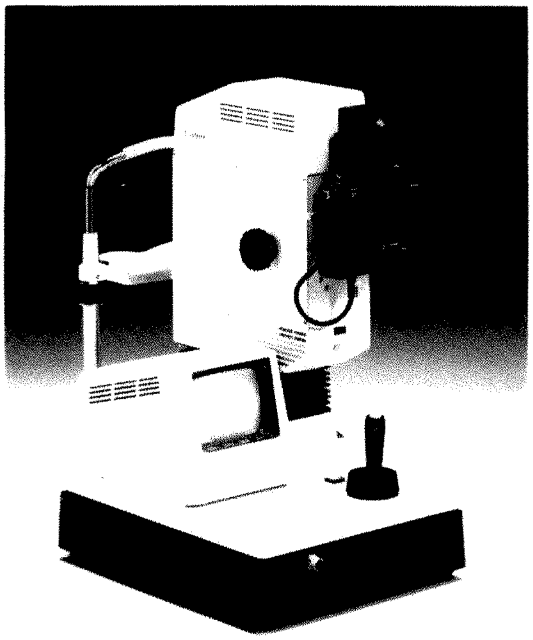

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British Journal of Ophthalmology, 1989, **73**, 461–462

Rapidly expanding exophthalmos: an unusual presentation of small cell lung cancer

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From the [1]Ophthalmology Service, the [2]Oncology Service, and the [3]Pulmonary Service of Landstuhl Army Regional Medical Center, and the [4]Ophthalmology Service of the Wiesbaden Air Force Regional Medical Center, Federal Republic of Germany

SUMMARY A 61-year-old male presented with a rapidly progressive exophthalmos from small cell lung cancer metastatic to the right orbit. His vision in that eye was 20/200, and his intraocular pressure was 36 mmHg. The orbital metastasis responded dramatically to chemotherapy. One week after starting the chemotherapy the patient did not have exophthalmos, his vision was 20/20, and three weeks later the intraocular pressure was 12 mmHg.

Small cell lung cancer (SCLC) is one of the most aggressively metastatic tumours.[1] It is the fifth leading cause of cancer death in the US, and only 1 to 2% of patients with disseminated disease at diagnosis achieve lasting remissions.[2] This report describes a patient who presented with a rapidly progressing exophthalmos from an SCLC and his good response to chemotherapy.

Case report

A 61-year-old white male developed acute swelling of his right eyelids, and a diagnosis of preseptal cellulitis was made. The patient did not respond to antibiotics, so he was referred for further examination and treatment. On presentation he had a fullness of the right eyelids and temporal fossa. The globe was proptosed by about 10 mm and embedded in an indurated tumour mass that raised the conjunctiva. The preauricular node was enlarged on the right. The visual acuity was 20/200 in the right eye, 20/30 in the left eye, and there was a 2+ afferent pupillary defect in the right. The intraocular pressure was 36 mmHg in the right eye and 12 in the left.

Computed tomography of the orbit (Fig. 1) revealed a large homogeneous tumour in the right temporal fossa that continued round the edge of the right orbital margin into the orbit to the superior orbital fissure. The tumour extended round the medial part of the eye and encompassed the lacrimal sac. The posterior part of the globe was distorted, apparently because it was tethered by the stretched optic nerve. Chest roentgenography (Fig. 2) showed a widened mediastinum with asymmetrical bilateral hilar adenopathy.

A biopsy of the right lateral edge of the orbit revealed metastatic SCLC. We had planned to administer radiation therapy to the orbit for palliation, but our hospital does not have radiotherapy

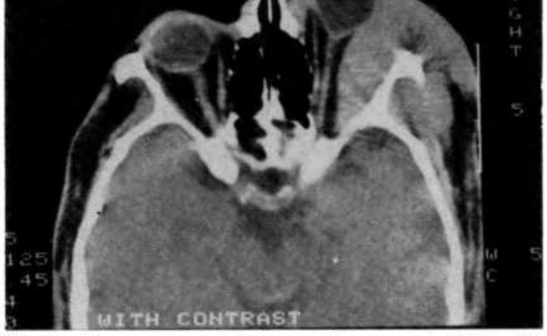

Fig. 1 *Pretreatment axial computed tomograph (CT) with contrast of the orbits. The eye, embedded in tumour, is deformed by compressive effects and by tethering of the optic nerve. The optic nerve has some redundancy in the orbit, and so it usually does not lie in one plane (left eye). The right optic nerve is stretched taught.*

Correspondence to Richard F Spaide, MD, Box 27, Landstuhl Army Regional Medical Center, APO NY 09180, USA.

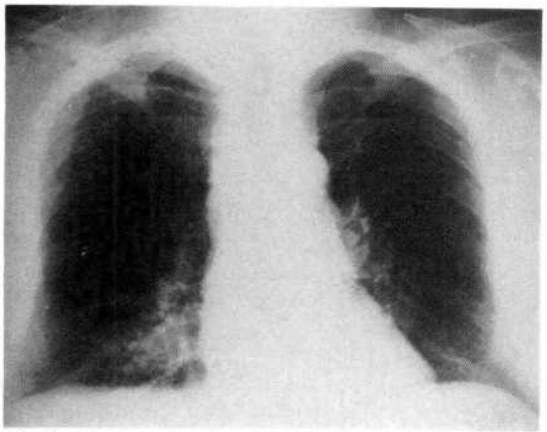

Fig. 2 *Pretreatment chest x-ray showing widening of the mediastinum, right paratracheal and aortopulmonic window abnormalities, minimal air bronchograms, and bilateral plural effusions.*

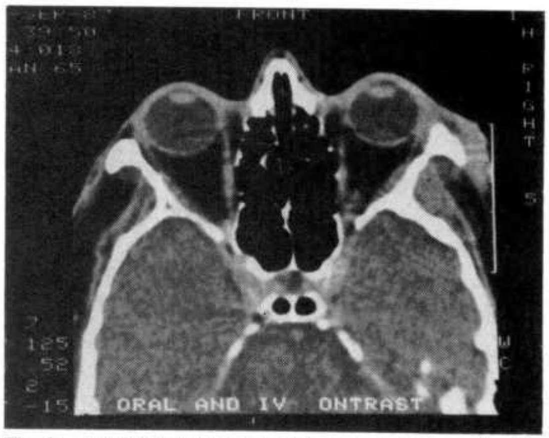

Fig. 3 *Axial CT of the orbits with contrast three weeks after the initiation of treatment showing the resolution of the exophthalmos, with a normal ocular morphology. Thickening remains in the temporal fossa and adjacent to the lateral orbital tubercle.*

capabilities, and scheduling problems would have delayed treatment for one week. In the interim we administered induction chemotherapy directed against small cell lung cancer: Cytoxan (cyclophosphamide) 1000 mg/m^2 on day 1, Adriamycin (doxorubicin) 45 mg/m^2 intravenously on day 1, VP 16 (etopside) 80 mg/m^2 intravenously on days 1, 2, and 3. The orbital tumour had a good response to the chemotherapy. At one week after starting therapy he had minimal thickening of the lateral orbital rim and a faint subconjunctival infiltration. He had no proptosis; he was orthophoric in all fields of gaze, and his visual acuity was 20/20. The primary tumour in the lung completely resolved after three cycles of chemotherapy. The computed tomograph of his orbit showed a resolution of the tumour mass (Fig. 3). The intraocular pressure was 12 mmHg three weeks after treatment started.

Discussion

We wanted to treat this patient with radiation, but this proved unnecessary. Since patients with SCLC have to be treated with chemotherapy anyway, it might be better to start the chemotherapy immediately and use radiation therapy only if chemotherapy proves unsuccessful. Indeed, at one time superior vena caval obstruction in small cell lung cancer was considered a medical emergency requiring immediate radiotherapy, but now induction chemotherapy is the treatment of choice.[3] We know of no other case of an orbital metastasis from SCLC treated with chemotherapy, but a previous report described a patient with SCLC metastatic to the iris who also had a striking response to chemotherapy.[4]

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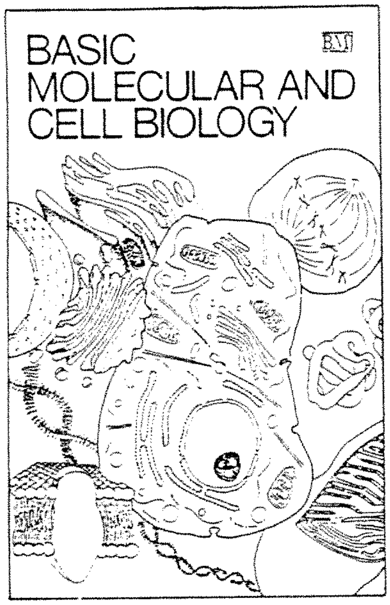

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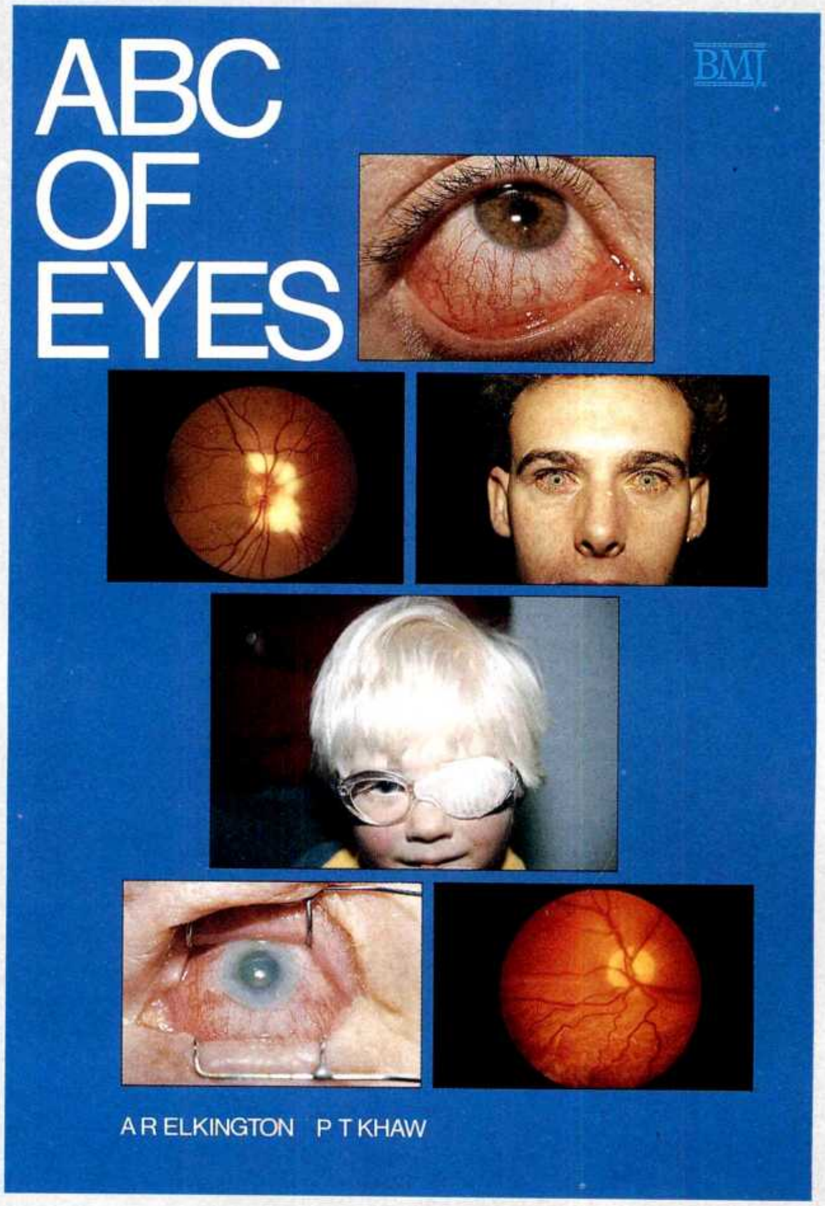

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British Journal of Ophthalmology, 1989, **73**, 463–467

Inflammatory pigmented paravenous retinochoroidal atrophy

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From the [1]*Department of Ophthalmology, School of Medicine, Tohoku University, Sendai, and* [2]*Tanifuji Eye Clinic, Morioka*

SUMMARY A 47-year-old Japanese man had a progressive degeneration of the retina and choroid along the retinal veins associated with uveitis of two years' duration. The lesion was characteristic of paravenous retinochoroidal atrophy: a contiguous atrophy of the retinal pigment epithelium and choroid of one-half to one disc diameter in size was present along most of the veins from the posterior pole to the far periphery. Fluorescein angiography showed a window defect in the retinal pigment epithelium, with hyperfluorescence representative of retinal pigment epithelium and choriocapillaris degeneration. Good visual acuity was attained after extracapsular cataract extraction for complicated cataract and vitrectomy for severe vitreous opacity had been performed in both eyes. The cause of this new inflammatory disease was unknown.

Pigmented paravenous retinochoroidal atrophy[1-4] is a rare condition in which the atrophic areas extend one-half to one disc diameter on either side of the vein and follow the vein's course, even when it branches. The cause of the condition is still unknown.[5-9]

We examined a patient who had gradually progressive paravenous retinochoroidal atrophy accompanied by an active panuveitis of more than two years' duration. We believe ours is the first report to describe active inflammatory causes of paravenous retinochoroidal atrophy.

Case report

A 45-year-old Japanese man was examined by one of us (YT) on 3 March 1985 and found to have had bilaterally blurred vision for six months His family and past history were uneventful. Ophthalmic examination showed his best corrected visual acuity to be 20/25 in both eyes. Slit-lamp examination disclosed keratic precipitates, cells in the anterior chamber, and floaters in the anterior vitreous. Fundus examination showed small, patchy, multifocal cobblestone-like areas of retinal pigment epithelial degeneration along the retinal veins in both eyes and round the optic disc (Fig. 1)

Although the patient was treated with systemic and locally administered corticosteroids, the uveitis persisted without improvement With the development of iridic posterior synechiae, complicated cataract of both lenses and the opacity of the vitreous increased, and the patchy retinal pigment epithelial degeneration enlarged to form contiguous lesions.

The patient was referred to Tohoku University Hospital on 6 April 1987. Ophthalmic examination disclosed a best corrected visual acuity of 20/200 in both eyes. Slit-lamp examination showed posterior synechiae of the iris, a few cells in the anterior chamber, and complicated cataract in both eyes. The fundi were obscured by severe vitreous opacity. A scotopic electroretinogram with single white-flash stimulation showed reduced a wave and b wave amplitudes (Fig. 2). Electro-oculography showed low standing potential and no response to light bilaterally.

The patient was admitted to hospital on 16 April 1987 Extracapsular cataract extraction and simple vitrectomy were performed in the right eye on 18 May and 5 June, and in the left eye on 23 June and 7 July. Systemic and local corticosteroids were administered postoperatively. The corrected visual acuity in both eyes was 20/20. The Humphrey field analyser

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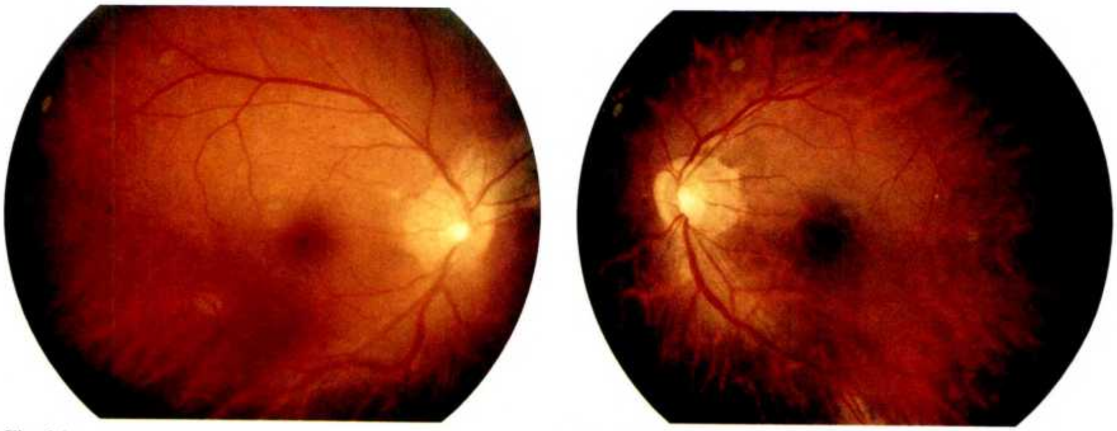

Fig. 1A Fig. 1B

Fig. 1. *Fundus photograph from 3 March 1985.* A: *Right fundus shows retinochoroidal atrophy round the optic disc, along the superonasal vein, and in the retinal veins two disc diameters inferotemporal to the macula.* B: *Left fundus had retinochoroidal atrophy around the disc and in the vein just temporally to the macula.*

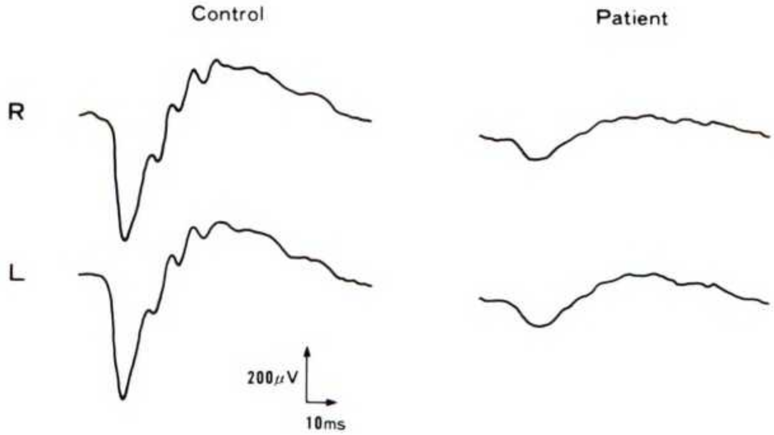

Fig. 2 *Right scotopic electroretinogram (ERG) with single white flash stimulation of 20 ms after 20 minutes of dark adaptation, pupillary dilatation, and topical anaesthesia (0·5% proparacaine hydrochloride). In both eyes* a *and* b *waves were reduced. Control illustrates normal responses on ERG.*

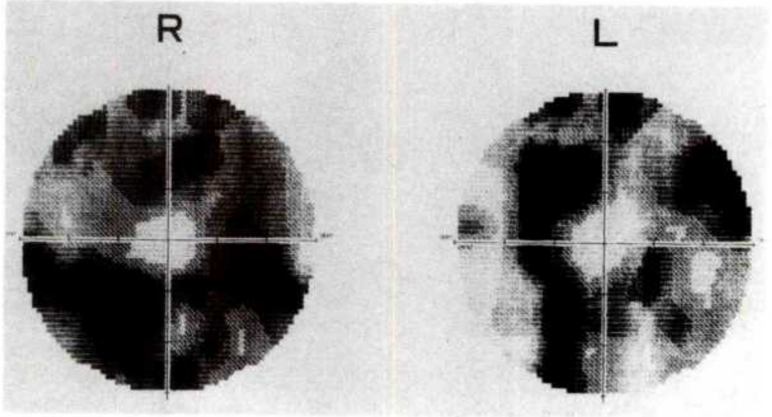

Fig. 3 *Humphrey field analyser showed geographic scotoma and an enlarged blind spot in both eyes.*

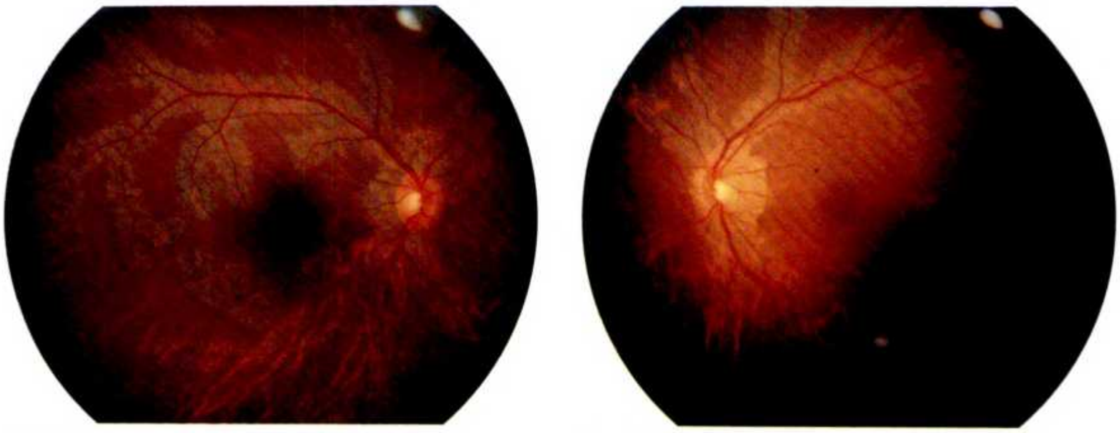

Fig. 4A

Fig. 4B

Fig. 4 *Fundus photograph from 26 September 1987.* (A) *Right and* (B) *left eyes. The degeneration progressed to form a continuous lesion along most of the veins in both eyes.*

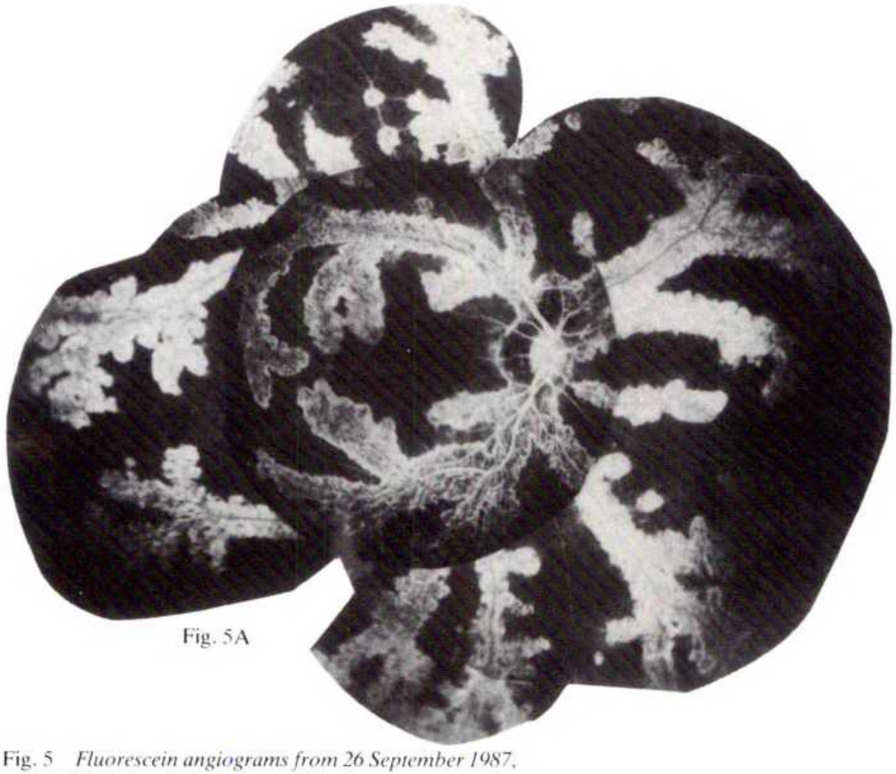

Fig. 5A

Fig. 5 *Fluorescein angiograms from 26 September 1987, of the* (A) *right and* (B) *left eyes. The degeneration of the retinal pigment epithelium and choriocapillaris is obvious along the retinal veins and round the optic disc.*

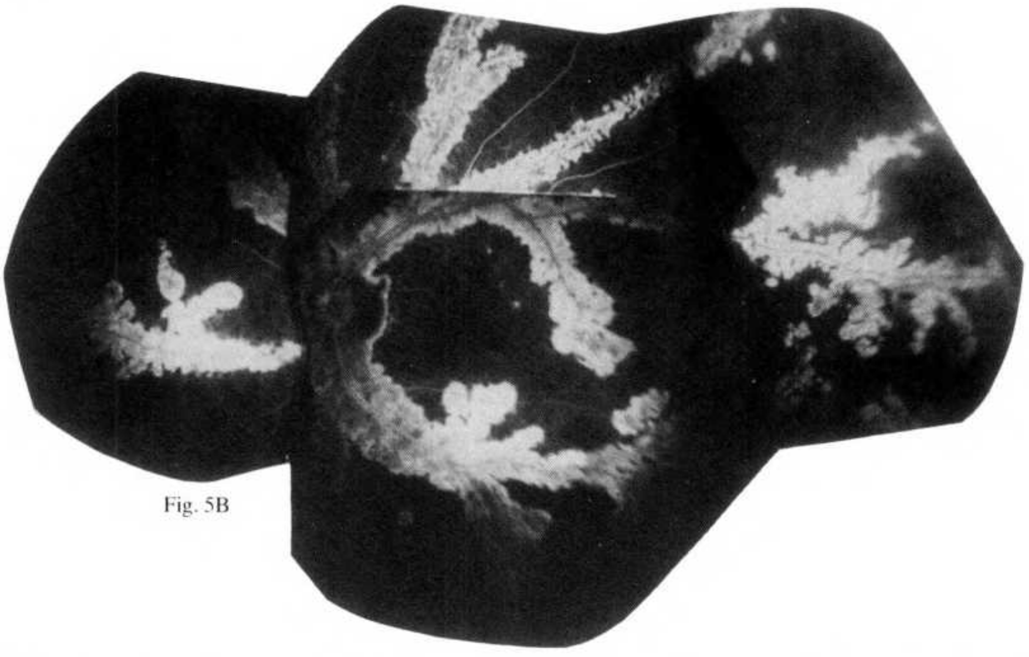

Fig. 5B

disclosed geographic scotoma (Fig. 3). A test of colour vision with Ishihara pseudoisochromatic plates was completed without error. Both fundi showed contiguous delimited atrophy of the retinal pigment epithelium along most of the retinal veins and round the optic disc. The atrophic regions were of almost the same size, and there were few clumps of pigment in the peripheral regions (Fig. 4). Fluorescein angiography in the early phase revealed a window defect of retinal pigment epithelium and choriocapillary atrophy that disclosed a large choroidal vasculature. In the late phase the degenerative area along the veins showed homogeneous hyperfluorescence (Fig. 5).

No systemic abnormality was found. Results of laboratory studies included normal complete and differential blood cell counts, serum amino acids, serum electrolytes, serum protein electrophoresis, erythrocyte sedimentation rate, and angiotensin converting enzyme. There was no serological evidence of syphilis, toxoplasmosis, systemic lupus erythematosus, or rheumatoid arthritis. A skin test for tuberculosis was within the normal range, as were serum antibody levels for herpes simplex virus, herpes zoster virus, cytomegalovirus, and measles virus.

Discussion

This patient's fundi and visual function were characteristic of pigmented paravenous retinochoroidal atrophy. The clinical course, however, was unique. To our knowledge there have been no reports of active inflammation with this disease. It was obvious, however, that inflammation had a major role in the pathogenesis of the retinochoroidal atrophy in our patient. Also unique to this patient was a small patchy area of atrophy that progressed to continuous lesions along the veins over a three-year period; Pearlman and colleagues[7] have reported the disease as being progressive.

Thus we believe that this case represents a new type of inflammatory disease of unknown origin marked by a progressive degeneration of the retinal pigment epithelium and choroid that occurs along the retinal veins. The main region to be affected was the retinal pigment epithelium. That was clearly demonstrated by fluorescein angiography and supported by an extinct pattern on the electro-oculogram.

The differential diagnosis includes both chorioretinal degeneration and inflammatory disease that cause chorioretinal atrophy, such as gyrate atrophy of the choroid and retina,[10] helicoid peripapillary chorioretinal degeneration,[1] choroiditis proliferans,[11] sarcoidosis, syphilis, acute retinal necrosis, cytomegaloviral retinitis, tuberculous disseminated choroiditis, onchocerciasis, toxoplasmosis, and frosted branch angiitis.[12] These clinical features, however, were different from those in our case.

Although steroid therapy cleared up the anterior and postoperative uveitis in our patient, it did not help the inflammatory pigmented paravenous retinochoroidal atrophy.

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Adverse effect of intraoperative phenylephrine 10%: case report

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SUMMARY The case is reported of a patient who suffered severe acute hypertension, cardiac arrhythmia, and myocardial infarction probably as a direct effect of phenylephrine overdose. Instillation of the drops during surgery probably enhanced the systemic absorption of a significant amount of the drug. Therefore it should be used during surgery with caution, especially in elderly patients and those with cardiovascular disease.

Phenylephrine hydrochloride is a commonly used mydriatic agent. While the cardiovascular effect of parenteral phenylephrine is well known, serious complications from its topical use are rare and are believed to be due to an idiosyncratic reaction. This report presents a case of phenylephrine induced systemic side effects due to overdosage.

Case report

A 57-year-old man had a total retinal detachment in the left eye. He had no known cardiovascular disease. On admission to hospital his blood pressure was 120/80 mmHg. His pulse rate was 80 per minute and the electrocardiogram (ECG) was entirely normal. Phenylephrine 10% and homatropine 2% were instilled in both eyes, one drop each every half hour for two hours. His preoperative blood pressure was recorded as 120/80 mmHg.

Under general anaesthesia the eye was encircled with a silicone strip. During subretinal fluid release the eye became soft and the pupil constricted. Intraoperative phenylephrine 10% was instilled, but four drops were administered inadvertently. Within minutes his blood pressure rose to 260/120 mmHg. The ECG monitor recorded ventricular bigeminy and multifocal ectopic beats.

Intravenous lignocaine 50 mg was given to correct the arrhythmia. The blood pressure dropped gradually to 120/80 mmHg over 30 minutes. Three hours after reversal of anaesthesia he complained of chest pains. The ECG showed widespread T wave inversion in leads I, II, AVL, and V1 to V6. He was treated as having an acute myocardial infarction. Two days later ST elevation was noted in leads V1 to V4. Serial testing of cardiac enzymes showed a rise in creatinine phosphokinase levels.

Further management was uncomplicated and he recovered eventually. The final diagnosis was that the patient suffered a non-Q-wave anterolateral myocardial infarction which was most probably due to the sudden alpha-sympathetic stimulation intraoperatively.

Prior to this episode he had an uneventful right cataract extraction. His preoperative blood pressure then was 140/90 mmHg. He had topical homatropine 2% and phenylephrine 10%, one drop each every half hour for two hours. No rise of blood pressure was recorded during the entire duration of the operation or in the postoperative period.

Discussion

Phenylephrine is a sympathomimetic drug which is a powerful alpha-receptor agonist with no beta-receptor activity. Parenteral phenylephrine causes increase in systolic and diastolic blood pressure due to peripheral vasoconstriction. Topical phenylephrine can cause a similar effect because it is absorbed rapidly via the conjunctiva and nasal mucosa.[1] Heath and Geite[2] had shown that topical phenylephrine 10% can increase the blood pressure up to 10 mmHg in 2% of subjects tested. However, a marked acute rise in blood pressure is thought to be an idiosyncratic reaction in a small subpopulation, because reports of such side effects are rare despite

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the widespread use of phenylephrine as a mydriatic agent

This case is different in that the severe reaction was probably due to overdosage rather than hypersensitivity, for the patient had had topical phenylephrine on two previous occasions without any rise in blood pressure. The dose received on this particular occasion was very high. If the average drop size is 0·05 ml, each drop of phenylephrine 10% would contain 5·0 mg. This patient had four drops, which is equivalent to 20 mg. Under anaesthesia, with the eyelids kept apart with a speculum and the conjunctiva opened extensively, a considerable part of the phenylephrine would have been absorbed via the exposed soft tissues. As the accepted safe dose of intravenous phenylephrine is only 1·5 mg, the dose that this patient was exposed to would probably be sufficient to cause a direct effect.

The adverse side effects associated with phenylephrine are severe acute hypertension, cardiac arrhythmia, myocardial infarction, and subarachnoid haemorrhage.[3] In a review of 33 cases of phenylephrine induced side effects[4] 15 had myocardial infarctions. Their average age was 71 years, and nine had a previous history of cardiovascular disease

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Autosomal juvenile retinoschisis without foveal retinoschisis

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SUMMARY We describe hereditary retinoschisis without foveal retinoschisis in a girl (the product of a consanguineous marriage) and her father. The father had peripheral retinoschisis with dendritic changes of the retina and good visual acuity. The daughter had peripheral retinoschisis complicated by vitreous haemorrhage and retinal detachment. Neither had foveal retinoschisis. The pattern in a scotopic single-flash electroretinogram differentiated this condition from other forms of retinoschisis. We believe that these cases represent the autosomal recessive form of juvenile retinoschisis without foveal retinoschisis.

Autosomal juvenile retinoschisis[1] is a rare vitreoretinal dystrophy characterised by peripheral retinoschisis without pathognomonic foveal retinoschisis. We describe a father and daughter who had peripheral retinoschisis without foveal retinoschisis, which possibly was transmitted as an autosomal recessive disorder. The results of a scotopic single-flash electroretinogram showed a slightly reduced a wave, a diminished b wave that returned to above baseline levels, and diminished oscillatory potentials, a pattern considered pathognomonic in this disorder

Case reports

CASE 1

A 2-year-old girl suffered a fall on 16 May 1987. Several days later her mother noticed the presence of right esotropia. The child was referred to Tohoku University Hospital because of a vitreous haemorr-

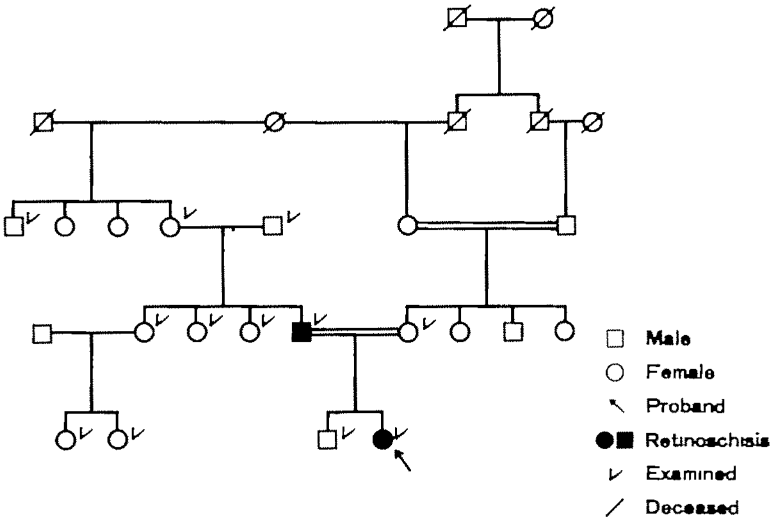

Fig. 1 *Pedigree of the affected family The proband is the product of a consanguineous marriage.*

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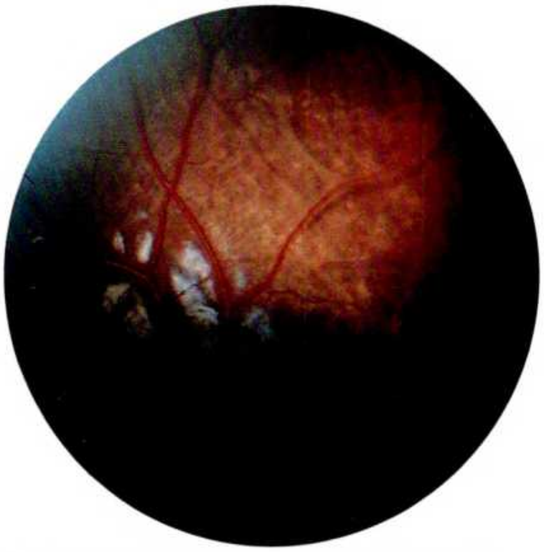


Fig. 2 *The left inferotemporal peripheral fundus of the proband shows retinoschisis and a large break in the inner layer of the retina.*

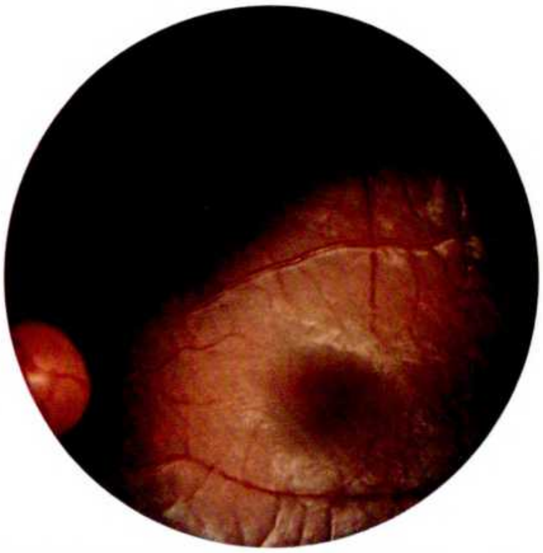


Fig. 3 *The left macula of the proband appeared normal, and no foveal retinoschisis is observed.*

hage in the right eye on 27 May 1987. She was the product of an uneventful pregnancy resulting from a consanguineous marriage (Fig. 1). Her physical and mental development had been normal.

The ophthalmic examination showed 15 prism dioptres of right esotropia and normal eye movements. The pupil was normal in shape and showed a normal light reflex. Visual acuity could not be measured because of the patient's youth. The right fundus was difficult to see owing to vitreous haemorrhage. The left fundus showed peripheral retinoschisis with inner retinal holes at the equator (Fig. 2). The macula appeared normal, and no foveal retinoschisis was observed (Fig. 3). A scotopic single-flash electroretinogram, which was recorded after 20 minutes of dark adaptation, displayed a slightly reduced a wave, a diminished b wave that returned to above baseline levels, and diminished oscillatory potentials (Fig. 4). Ultrasonography disclosed a strong sheet-like echo that was suggestive of a retinal detachment.

After a week's observation an ophthalmoscopic examination of the girl's right eye showed a small, full-thickness retinal detachment that involved the inferotemporal retina and extended from the 5 to 9 o'clock meridian. Also observed were a large grey membrane floating in the inferotemporal vitreous cavity and two holes in the outer retinal layer at the 6 o'clock meridian between the vascular arcade and equator, among the old vitreous haemorrhage. Another lesion of retinoschisis spread across the superotemporal fundus. The optic disc appeared normal, and foveal retinoschisis was not observed.

Surgical treatment consisting of cryoretinopexy and scleral buckling was performed successfully on 9 June 1987. The retina became reattached during the postoperative period of observation.

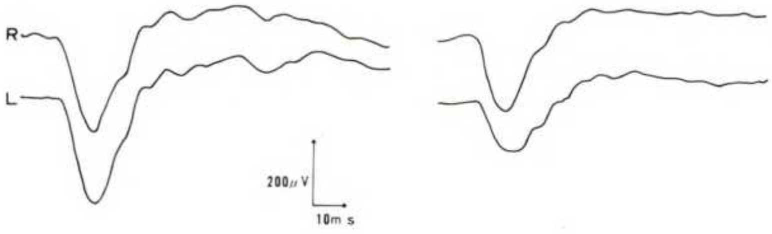


Fig. 4 Right: *Single-flash electroretinogram, measured after 20 minutes of dark adaptation, shows a normal* a wave*, a reduced* b *wave that returned to above the baseline levels, and diminished oscillatory potentials in the proband.* Left: *An electroretinogram from a normal 2-year-old, measured after 20 minutes of dark adaptation.*

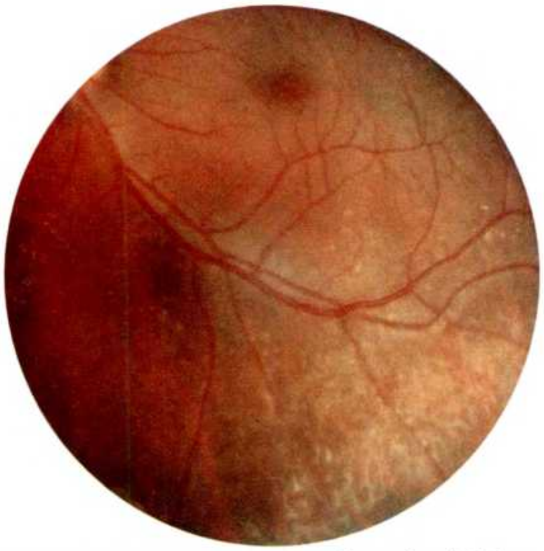


Fig. 5 *The left peripheral fundus of the proband's father discloses dendritic filariform structures of the inner retina. The macula appears intact, and foveal retinoschisis is absent.*

CASE 2

The 35-year-old father of the proband was examined on 27 May 1987. His best corrected visual acuity was 20/20 in both eyes. Colour differentiation assessed with Ishihara plates, intraocular pressure measured by Goldmann tonometry, and anterior segments examined by slit-lamp biomicroscopy appeared normal in both eyes. Each fundus demonstrated peripheral retinoschisis and dendritic filariform structures in the inner layer of the schisis. No foveal retinoschisis was observed (Fig. 5). Visual field examination by Goldmann perimetry showed absolute depressions in the peripheral fields in both eyes.

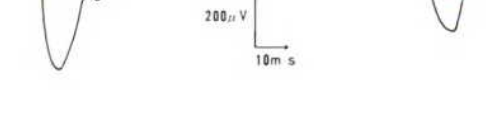
A scotopic single-flash electroretinogram, recorded after 20 minutes of dark adaptation, displayed a slightly reduced a wave, a diminished b wave that returned to above baseline levels, and diminished oscillatory potentials (Fig. 6). Fluorescein angiography disclosed arborescent figures of retinal vessels in the regions of retinoschisis.

Discussion

Among the various hereditary retinoschises foveal retinoschisis is an important pathognomonic finding. In X-linked juvenile retinoschisis, which is carried by the X chromosome and is transmitted in a recessive manner with a high degree of penetrance, foveal retinoschisis occurs in 98% to 100% of patients. In approximately 50% of patients foveal retinoschisis is the sole pathological finding.[2] This disease is characterised by a negative electroretinogram, which showed a normal a wave, a b wave that does not return to the baseline values, and reduced oscillatory potentials.[3] In a female carrier of X-linked juvenile retinoschisis radial wrinkling of the inner limiting membrane occurs around the fovea, but no peripheral retinoschisis is seen.[4] The electroretinogram is normal. Favre-Goldmann disease,[5] which is inherited in an autosomal recessive manner, is not only characterised by peripheral retinoschisis and foveal retinoschisis but also includes an optically empty vitreous, chorioretinal atrophy, cataract, loss of peripheral vision, glial bands, eventual blindness, and an extinguished electroretinogram. In autosomal recessive foveal retinoschisis[6] the lesion is limited to the macular area. The electroretinogram is normal. Autosomal dominant juvenile retinoschisis[7] sometimes affects the macula. In eight patients described by Yassur and colleagues[7] three presented with foveal retinoschisis and five had macular pigmentary changes. Six patients had a normal single electroretinogram; the remainder had anormal a wave and a reduced b wave that returned to above the baseline levels.

Hereditary retinoschisis without foveal retino-

Fig. 6 Right: *A single-flash electroretinogram of the proband's father, measured after 20 minutes of dark adaptation, demonstrates a normal* a *wave, a reduced* b *wave that returned to above baseline levels, and diminished oscillatory potentials.* Left: *An electroretinogram from a normal 35-year-old, measured after 20 minutes of dark adaptation.*



schisis is diagnostic for autosomal juvenile retinoschisis.[1] Cibis[1] described a family in which female monozygotic twins and their grandmother had peripheral retinoschisis without foveal retinoschisis. Their disorder was considered an autosomal form of retinoschisis with recessive or possibly even dominant transmission of inheritance. The father and daughter described here have retinoschisis without foveal retinoschisis All members of the family live in a small, remote village. At least two consanguineous marriages have been recorded in the pedigree. Because the girl described in this report is also the product of a consanguineous marriage, the most likely mode of transmission in this family is autosomal recessive. The absence of foveal retinoschisis and the electroretinographic pattern displayed by the father and daughter also differentiate this condition from other forms of vitreoretinal dystrophy.

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'In-the-bag' hyphaema—a rare complication of posterior chamber lens implantation

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SUMMARY A 72-year-old woman developed a hyphaema on the first postoperative day after a combined trabeculectomy and extracapsular cataract extraction with posterior chamber intraocular lens implantation. On the second day the blood had redistributed to accumulate 'in the bag' posterior to the intraocular lens and had formed a fluid level. Postural drainage helped to clear the hyphaema from both locations, with no short-term effect on visual function or the filtering bleb.

Coexisting cataract and glaucoma are frequently managed by combining a trabeculectomy with an extracapsular cataract extraction and posterior chamber lens implantation (triple procedure).[1-3] A postoperative hyphaema may occur in 6–27% of such cases and usually resolves spontaneously.[1-3] Rarely the hyphaema may last longer or require surgical intervention.[4,5] We describe an unusual type of hyphaema which followed a triple procedure.

Case history

A 72-year-old woman with open-angle glaucoma and immature senile cataract was admitted to the hospital for combined trabeculectomy and extracapsular cataract extraction with posterior chamber lens implantation. The glaucoma was poorly controlled on medical therapy. She was on irregular treatment with soluble aspirin for low backache but had not recently taken any.

She underwent an uncomplicated triple procedure in the right eye. The trabeculectomy flap was fashioned at the upper nasal end of the corneoscleral section. An endocapsular technique was used for the cataract extraction, and the lens was placed in the capsular bag.

On the first postoperative day she was found to have a hyphaema filling one-third of the anterior chamber. There was a good filtering bleb and the intraocular pressure was 4 mmHg in the operated eye. The vision was 6/36 and the fundus, though hazily visible, appeared normal. The hyphaema was managed conservatively with limited bed rest and topical treatment comprising maxidex eye drops (dexamethasone 0·1%, hypromellose 0·5%) and chloromycetin four times a day and cyclopentolate 1% eye drops twice a day to the operated eye. Topical antiglaucoma treatment was continued in the unoperated left eye. Over the next three days, while the anterior chamber hyphaema remained relatively static, blood accumulated posterior to the intraocular lens, in the capsular bag, where it formed a fluid level (Fig. 1), and visual acuity decreased to 2/60. After 10 days' conservative treatment with no improvement postural drainage was attempted. The patient was nursed in the left lateral position with the foot end of the bed raised. The blood in the anterior chamber cleared in a matter of hours, and the blood behind the lens cleared almost entirely over the next two days. The visual acuity improved to 6/24 unaided at this stage and the intraocular pressure was 8 mmHg. One month later the corrected visual acuity was 6/9, with a good bleb and an intraocular pressure of 10 mmHg. A few red blood cells on the posterior surface of the lens inferiorly, well below the visual axis and posterior synechiae, were the only residua of the hyphaema (Fig. 2).

Discussion

Our case shows several interesting features. Firstly, the capsular bag is an unusual location for a postoperative hyphaema. We have been unable to find a similar report in the literature. An endocapsular

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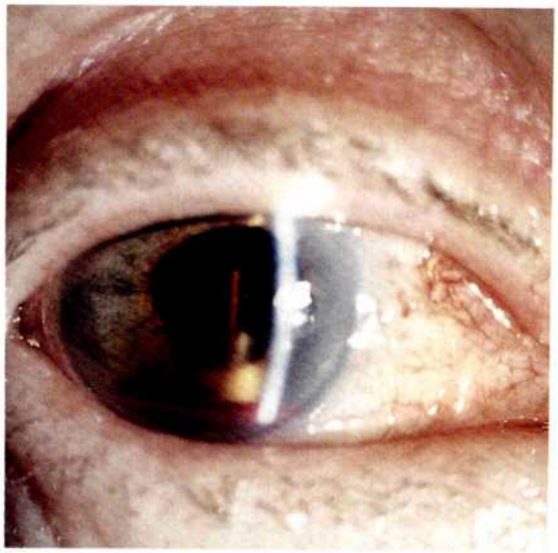

Fig. 1 *Slit-lamp photograph of the right eye showing a hyphaema, the intraocular lens in the capsular bag, and accumulation of blood forming a fluid level behind the lens.*

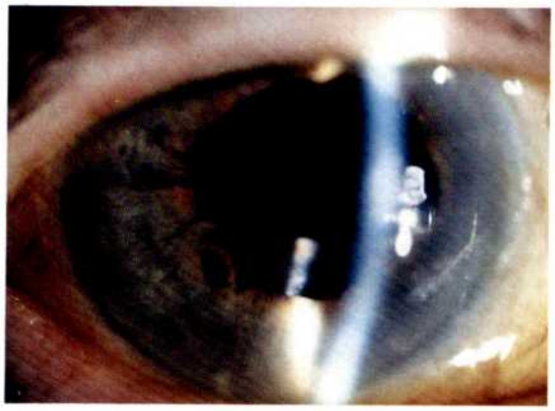

Fig. 2 *Slit-lamp photograph of the right eye at the first postoperative visit showing posterior synechiae and a granular appearance in a line behind the intraocular lens. The granular appearance is caused by red blood cells adhering to the back of the intraocular lens.*

technique with an 'in-the-bag' placement of an intraocular lens leaves a large anterior capsular flap in front of the lens and may more readily predispose to an in-the-bag hyphaema. Blood could thus seep through to accumulate within the capsular bag before the anterior capsular edge adhered to the lens. With conventional extracapsular extraction and planned ciliary sulcus fixation most of the anterior capsule is excised, and this measure, together with the intraocular lens in front, may preclude such an accumulation.

Secondly, conservative management having failed, postural drainage cleared the blood from both locations. The presence of blood in such close proximity to the posterior capsule is of some concern, as it may incite opacification. We waited 10 days before attempting postural drainage, as we felt that prolonged periods in an awkward position would be difficult for an elderly person.

Thirdly, locating the trabeculectomy flap at one end of the cataract incision was of benefit, as the hyphaema could be drained without the risk of red blood cells adhering to the lens surface. Other surgeons[3] position the trabeculectomy flap in a similar manner, determined by the design of intraocular lens that they use. We find that siting the scleral flap at one end is technically easier, and in this case facilitated the postural drainage.

In summary, we have described a case of an unusual postoperative hyphaema following a triple procedure. Postural drainage is of benefit in the management of hyphaemas, even those occurring in the bag, and is facilitated by positioning the trabeculectomy flap to one side.

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Correspondence

Uveal melanoma management

Sir, Two important unresolved issues in uveal melanoma management are: at what stage in the natural history of the disease must intervention occur to avoid development of metastases, and what is the most effective means of treating this tumour? While there are no definitive data that demonstrate that either irradiation or enucleation is superior in preventing tumour-related mortality in uveal melanomas, Professors Manschot and Van Strik have made some false statements and inaccurate assumptions in their paper[1] to marshal the argument that enucleation is better.

A number of assumptions about behaviour of uveal melanomas are backed by tenuous, if any, data The doubling times of either primary or metastatic melanomas are uncertain In primary eye tumours the doubling time may range from 30 to 360 days As we and others have shown, measurement of doubling times is difficult and these data must be analysed cautiously.[2,3] While Manschot and Van Strik are correct that Gass thought melanomas grow at a constant, slow rate prior to enucleation, our data showed a greater than exponential growth of tumour thickness in some uveal melanomas [4] In a few cases with simultaneous ocular and metastatic uveal melanoma, metastases often grow at strikingly greater rates than the primary neoplasm.

It is difficult to support a central tenet of their argument, that the shortest possible interval between dissemination of uveal melanoma and death from metastasis is three years, and that 'a period of less than four years' is irrelevant with regard to influence of ocular irradiation on survival While it is possible that many patients who die in that interval already have metastatic disease, others may not, and there are no methods at the present time to separate the two groups.

We strongly disagree with a second central point in Manschot and Van Strik's argument that if any tumour cells are still present after irradiation the melanoma is still active. This is analogous to the statement that if there is a body still present, despite the absence of vital signs, it is not dead. The goal of successful radiation is to destroy the reproductive integrity of a tumour. In some tumours cells appear viable at the light microscopic level but have lost their reproductive integrity Children who died of unrelated causes years after successful retinoblastoma irradiation can have viable appearing cells on histological examination of the treated eye In some uveal melanoma eyes, enucleated because of radiation complications after helium ion irradiation, we have observed neither mitoses nor evidence of cell cycling using bromodeoxyuridine studies [5] The statement that 'only regression can save a patient's life if metastases were absent prior to treatment' is incorrect.

In support of their hypothesis Manschot and Van Strik cite the findings of a study which were shown to be invalid. It is true that unadjusted survival of enucleated patients in Gass's study was better than that of radiated patients. However, patients treated by radiation were more likely to have anterior tumours, a known prognostic factor for analysis When these data were reanalysed using statistical methods which adjusted for this imbalance of prognostic factors, there was no longer any difference in survival between the two treatment types [6]

The statement that 'despite sufficient lapse of time, almost all survival statistics after irradiation are still based on follow-up periods of a few months to no more than three to four years' is incorrect We published the first 128 patients treated consecutively with protons with a median follow-up of 5·4 years (range, 2·7–10·5 years).[7] In this series the five-year survival data compare favourably with those of historical controls from previously published large series of patients who underwent enucleation [8–11]

The statement that 'patients have the right to be treated by enucleation which eliminates any further dissemination' is unsupportable. As the authors point out, there is a paucity of long-term data on large numbers of patients after irradiation of uveal melanomas. Short-term analysis of patients treated with either proton irradiation or cobalt plaques and compared with enucleation demonstrated no better survival with the latter technique when asymmetric factors were adjusted for.[6–11] We therefore believe that these authors fail to support their argument that enucleation is definitely better than irradiation Although long-term follow-up studies are necessary for definitive answers, present data indicate that irradiation has no deleterious effect on the likelihood of the development of metastasis.

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Is irradiation a justifiable treatment of choroidal melanoma?

Sɪʀ, In reply to the letter by Drs Char *et al.*, the answer to the question, 'at what stage in the natural history of the disease must intervention occur to avoid development of metastasis,' is. *at the earliest feasible one, preferably before the 7 mm diameter stage* (see paragraphs 3 of previous replies) [2,6] The answer on 'the most effective means of treating this tumour' is: *enucleation at the earliest feasible stage, this eliminates any (further) dissemination*. Irradiation of melanomas has been a regular practice for about 15–20 years The reason that 'there are no definitive data that demonstrate that either irradiation or enucleation is superior in preventing tumour-related mortality' is the surprising lack of reported ≥10-year survival results of irradiated patients Only one clinic has published prospective 10-year comparative survival results of all primary enucleated and irradiated patients in the same period.[1]

So far 39 calculated doubling times of uveal melanomas have been reported Paragraph 4 of our reply[2] to Drs Zimmerman *et al* [3] explains why it is warranted to assume that nearly all metastatic deaths within 6·1 years after treatment are a consequence of pre-existing dissemination

More than 50% of 153 microscopically studied irradiated melanomas did not reveal any necrosis, while 94% contained viable tumour tissue.[4] One wonders that ophthalmic radiotherapists, not being trained pathologists, claim to be able to interpret better the viability of melanoma cells, which presumably they have not studied, than trained pathologists who have studied these tumours Char *et al* state that they have not observed mitoses in some irradiated melanomas. Other pathologists and we have observed mitoses in proton beam and in ruthenium irradiated melanomas Besides, a body is legally dead because of the presence of signs of death, not because vital signs are absent

The findings by Gass in his 10-year follow-up of all patients have never been 'shown to be invalid' The main criticism is the greater number of anteriorly located melanomas in the irradiation group. Many believe, for no reason, that anterior melanomas have a worse prognosis Weinhaus *et al.*[5] found that 'patients with juxtapapillary melanomas had a worse prognosis than those with tumors in other locations'.

Our statement[6] '*almost all* survival statistics after irradiation are still based on follow-up periods of a few months to no more than three to four years' was correct at the time it was submitted (see paragraphs 7–9 of reply to Dr Oosterhuis *et al* [7]).

Our statement that 'patients have the right to be treated by enucleation which eliminates any further dissemination' is progressively becoming more supportable Death from metastases, disseminated after irradiation, cannot manifest itself before six years after therapy. 'Short-term analyses' of treated patients are irrelevant. Survival rates after enucleation, irradiation, and observation are identical during the first six post-treatment years if the selection conditions have been identical. Results more than six years after irradiation have been published only twice, both were highly unfavourable.[1,8]

After enucleation any (further) dissemination is prevented After irradiation major parts of the remaining tumour tissue (69% after a two-year follow-up period[4]) continue their growth and will shed cell emboli, eventually causing metastatic death after more than six years

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Familial exudative vitreoretinopathy (FEVR) and platelet dysfunction

Sɪʀ, Chaudhuri *et al* [1] reported abnormal platelet aggregation in patients from two families with familial exudative vitreoretinopathy (FEVR) However, Gole *et al.*[2] reported no platelet aggregation defects in a patient with incontinentia pigmenti, a separate syndrome with a phenotypically similar proliferative retinopathy These two conflicting findings are at odds with regard to association between FEVR and platelet function.

We have performed platelet aggregation studies on two patients with FEVR—a 7-year-old boy with total blindness and his 14-year-old female cousin, who is mildly affected The boy's total blindness at 3 months of age has been described elsewhere.[1] Neither subject had been exposed to any antiplatelet agents within the two weeks prior to the study Coagulation studies were conducted and the results compared with the normal ranges of values in our laboratory.[4] Platelet aggregation to added arachidonic acid (1·5 mmol/l), adrenaline (5 µmol/l), collagen (1 0 mg/l), ristocetin (1·5 g/l, 1·2 g/l, and 0 5 g/l) and adenosine diphosphate (ADP) (1 and 10 µmol/l) was within normal limits in each patient as compared with that of healthy controls. Platelet counts and morphology were normal, as were prothrombin times, partial thromboplastin times, and fibrinogen levels. Factor VIII and von Willebrand's factor were also within the normal range in each patient The only abnormality noticed was the boy's bleeding time of 13 minutes (normal range 2–9 minutes) and his lack of adenosine triphosphate (ATP) secretion as measured by the luciferin-luciferase method using a lumi-aggregometer. This finding is consistent with storage pool disease. The cousin's bleeding time and ATP secretion were normal

Although we found no abnormality of platelet aggregation in response to arachidonic acid in either patient, the prolonged bleeding time and storage pool disease in the boy may have aggravated his condition, resulting in his total blindness, which brought him to medical attention originally [1] An additional feature of his history may be significant. Shortly after his birth his mother reports being treated with high doses of aspirin for endometritis while breast feeding him The combination of FEVR, his storage pool disease, and aspirin exposure may explain his severe clinical course. While Chaudhuri *et al* 's report of platelet aggregation defects in response to arachidonic acid has yet to be verified in other FEVR patients, this case supports the contention that platelet abnormalities may contribute to the severity of FEVR

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Call it lentectomy

SIR, Congratulations to Drs Grossman and Peyman on the report of their very successful application of this procedure [1] Following Dr Peyman's pioneering work in this area we adopted his procedure and have been similarly gratified with a low rate of complications and very successful results.

Dr Peyman has been a persistent advocate of the term 'pars plicata', which is anatomically correct. Now if we can just get him to call it a len*t*ectomy, then he will have it 100% proper (Ectopia len*t*is[2] is another condition which is very well treated by his procedure.)

PAUL E ROMANO
Gainesville,
Florida,
USA

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SIR, I appreciate the kind comments of Dr Romano on our paper His suggestion is correct, and we will use the proper terminology

GHOLAM A PEYMAN
LSU Eye Center,
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USA

Eye protection for welders

SIR, Mr G P H Brittain emphasises the need for adequate eye protection at all times for amateur welding especially using the MIG welder (metal arc inert gas welder) [1] Fortunately the two patients reported on by Mr Brittain had a full visual recovery. We reported a case of foveal injury by an amateur welder[2] which produced permanent visual loss, further emphasising the potential seriousness of the injury that can occur.

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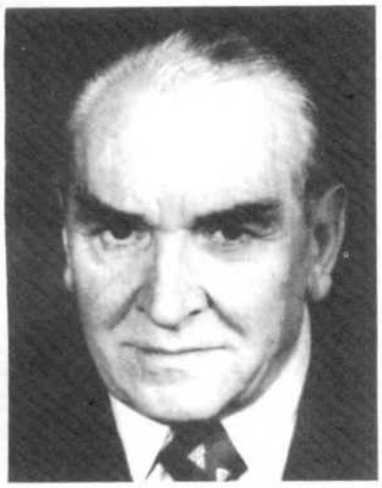
Obituary

Professor T Krwawicz

Professor Tadeusz Krwawicz, who died in September 1988 at the age of 78 years, was born in Lwow in 1910.

Initially he had started to study mining engineering following the example of his father and grandfather, but he soon realised that medicine was more attractive to him.



He entered the medical faculty at the University of Lwow and, graduating in 1938, became an assistant in the eye department of the university hospital. He remained in this position during the second world var and occupation first by Russia then by Germany nd finally again by Russia. During this last period e served with the Polish army as an ophthalmic ecialist in Lublin.

After demobilisation he became consultant thalmologist in the eye department of the newly ated University of Lublin and was promoted to ofessor in 1957. Apart from his important disovery of the use of cryo techniques in surgery he was lso responsible for leading research in the fields of biochemistry, immunology, corneal structure, and experimental refractive keratoplasty. In all he published more than 100 papers on these and related subjects, becoming a member of the Polish Academy of Science in 1957. However, it is for cryosurgery that he will be chiefly remembered.

Professor Krwawicz relates in his autobiography how the idea of cryoextraction came to him during experimental work on rabbits in which he was having difficulty achieving intracapsular lens extraction. He noticed the strength of the adhesion of a frozen probe to the lens and decided to try this method for lens extraction. After preliminary work on rabbits he progressed to human subjects, with the excellent results that surgeons trained from 1960 until the mid-1980s will recognise. (It is remarkable that many surgeons trained during the last few years may hardly have seen a cryoextraction, so rapid has been the switch to modern extracapsular techniques.) He published his method first at the Congress of Polish Ophthalmologists in 1960, where it was received with enthusiasm. The method was soon adopted widely, though his original method using 'dry ice' (carbon dioxide snow) and alcohol was sometimes misunderstood, so that ordinary frozen water was used. Eventually other types of cryoprobes were introduced, and the technique became virtually standard practice in many of the major centres of ophthalmology the world over. He spoke at the Oxford congress in 1965 and was greeted with applause.

Tadeusz Krwawicz was born and spent his early years in the country, so that his chief delights were country pursuits and a love of nature. He was never so happy as in the woods with his two beloved dogs enjoying the general atmosphere whether by night or day. The recipient of many awards and honours in both eastern and western Europe, he travelled widely in response to invitations from many parts of the world. He was the first president of the Cryo-ophthalmological Society. Sadly his wife died in an accident some years ago. His son also became an ophthalmologist. In Professor Krwawicz Poland has lost a great representative in world ophthalmology.

KG and JLR

Book reviews

The Retina: An Approachable Part of the Brain. By JOHN E DOWLING. Pp. 282. £29·95. Harvard University Press: London. 1987.

There are very few scientific books that fall into the category of 'I could not put it down' but this is one which most certainly does. Within its pages the reader is instantly captivated by the highly readable prose of an undoubted leader in the field of retinal physiology. John Dowling is, however, not only a distinguished research worker: he is also one of those few individuals whose intellect and understanding are coupled with the ability to teach, enthuse and stimulate his readers.

The book is a brilliant review of retinal physiology past and present and is written in such a fashion that students at all levels will find it invaluable. It starts with an overview of the ways in which research workers have utilised progressively more complex biological organisms in order to investigate the functions of neurones and ultimately the brain. In this initial review the role of the retina and vision research is highlighted, and the appropriateness of the book's subtitle immediately becomes apparent, as indeed the retina is an approachable part of the brain. Professor Dowling then goes on to give a thorough and systematic account of the retina and the ways in which modern research have begun to enable an understanding of its functions. He starts by giving a beautifully illustrated account of the various types of retinal neurones, their detailed anatomy, and their location. In this section he also enhances the morphological descriptions of retinal elements by interrelating them with a number of different aspects of information processing. This theme is further developed by accounts of the detailed wiring diagrams of the retina and the types of neuronal responses elicited by varying photic stimuli. Having built up this basic structural and functional picture of the retina the author goes on to consider suborders of complexity in dealing with the physical and biochemical aspects of information transfer at neuronal synapses, and the role of glial cells in maintaining retinal function, particularly in relation to the electroretinogram A chapter on photochemistry, phototransduction, and visual adaptation is a wonderful example of the author's ability to encapsulate complex information in a very short and highly digested form but one which examination students will find invaluable The final section of the book deals with the retina and the brain and current concepts of information interchange and processing in the higher visual centres.

To be critical of this book is very difficult. However, I think that it would have been helpful to have included a section on the retinal pigment epithelium and on the interrelationships between pigment epithelial cells, photoreceptor cells, and interphotoreceptor matrix. I think it would also have been even more helpful to the clinical reader to give some indications as to the sites of retinal malfunction in relation to retinal diseases where the electrophysiological responses are known to be atypical However, these comments are trivial, as the author may have deliberately excluded these subjects.

In summary, this is an excellent book, well written and illustrated. I thoroughly recommend it and I am sure it will be enjoyed by all who delve into it. JOHN MARSHALL

Surgery of the Eye. Vols 1 and 2. Eds S R WOLTMAN, R H KEATES, C S HOYT, B R FRUEH, J HERSCHLER, AND D M CARROLL. Pp. 1111. £195·00. Churchill Livingstone: Edinburgh. 1987.

In its two volumes and over 1100 pages this work is a compilation of the knowledge of some of the finest ophthalmologists practising today, though it must be admitted the list of authors is confined largely to those from the United States. For the most part the editors have achieved a remarkable consistency in style with the exception of the many fine line drawings, which do reflect the differing techniques of the six principal illustrators. The illustrations are copious and informative, and the lack of colour plates is hardly noticed at all Because each chapter is written by an acknowledged expert, the text becomes clear and effortless to read.

Inevitably there are omissions and for the most part they are not a serious detraction from the quality of the work. I personally would have enjoyed a chapter on surgical instrumentation and materials and a few introductory remarks on the simple but important subjects of incisions and correct suturing techniques It is impossible to discuss each chapter or even each section in the detail they deserve, but the purposes of this review can be served by my mentioning two sections, one in which I have a major interest and one in which my interest is perhaps less keen. The section on the cornea is well balanced ranging from penetrating keratoplasty to keratoprosthesis. (I was relieved to read that the author of the chapter did not have much enthusiasm for the latter technique) The chapter on lamellar keratoplasty was a welcome sight in an American textbook, though perhaps Waltman (the author) might have given a slightly better idea of how difficult the procedure is. 'Dissections down to Descemet's may be carried out' (!) Refractive surgery was covered in detail, though events have overtaken the chapter on epikeratophakia, since the experts no longer recommend keratectomy as part of the preparation of the host bed There is also a comprehensive chapter dealing with excision of pterygium by a technique that ought to prove effective It is a mark of the success of the book that despite the condensation of each aspect of ophthalmic surgery to a few chapters there is room for discussion of minutiae, the corneal section was no exception, with mention being made of iridoplasty during corneal grafting My main complaint about this section was that there was little discussion of the emergency corneal graft, which is a most difficult procedure for the infrequent corneal graft surgeon, yet it is precisely this surgery that the infrequent grafter is sometimes called upon to perform. By contrast I also found the chapters on photocoagulation clear and precise, and having read them I felt that even a first year senior house officer should have a good idea of the practicalities of retinal photocoagulation and in particular which patients would be likely to benefit and which patients would not

These volumes will soon be found on the bookshelves of most large eye departments throughout the English-speaking world. I would certainly recommend them to everyone, but I do hope the publisher will attempt to keep them up to date with frequent revisions in the future. It would be a pity to see such a fine work become obsolete

COLIN M KIRKNES

Notes

Immunopathology of intraocular inflammation

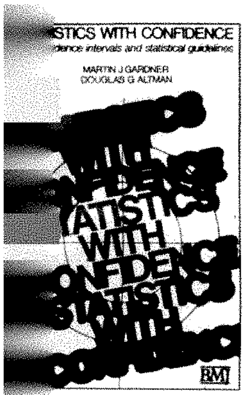
A symposium on recent developments in the immu pathology of intraocular inflammation will be held Amsterdam on 31 October to 3 November 1989. Detai from Dr A Kijlstra, Department of Ophthalmo-immunopathology, Netherlands Ophthalmic Research Institute, PO Box 12141, 1100 AC Amsterdam, The Netherlands.

Ophthalmic photography

An International Conference on Ophthalmic Photography (ICOP '90) will be held at Singapore on 14–17 March 1990. Details from Lawrence M Merin, RBP, Meeting Chairman ICOP '90, Cullen Eye Institute, Baylor College of Medicine, 6501 Fannin, Houston, Texas 77030, USA

Paediatric surgery

The 4th Steglitz Paediatric Surgical Symposium on 'Laser application in children' will be held in Berlin on 10–11 November 1989 at the International Congress Centre. Details from Dr Felix Schier, Department of Paediatric Surgery, Free University of Berlin, Hindenburgdamm 30, 1000 Berlin 45, West Germany.



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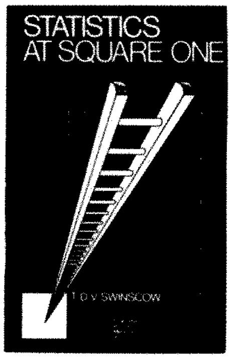

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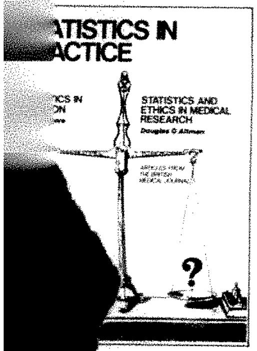
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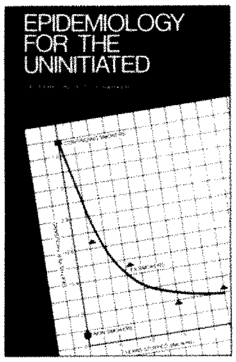

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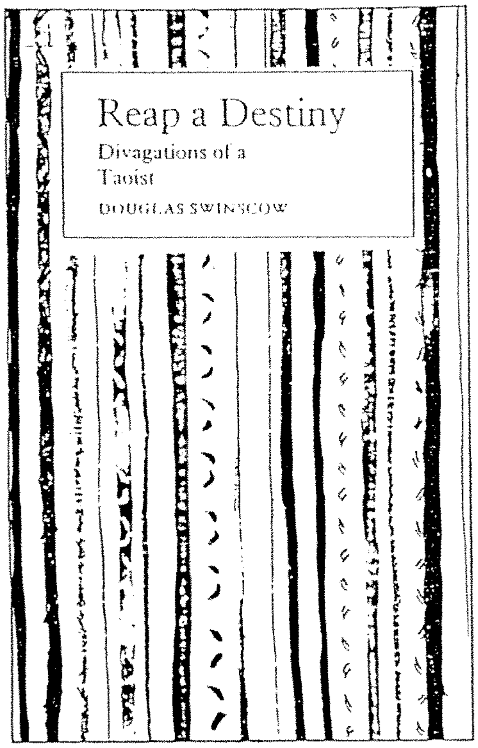
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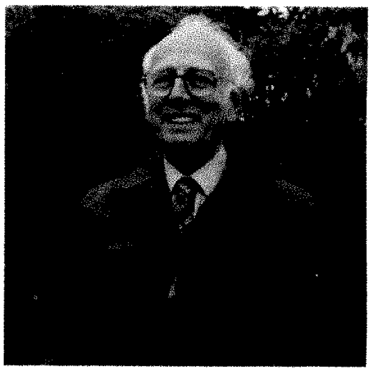

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